Predicting Weight-Related Outcomes in Healthy Adolescents: Clinical Applications of fMRI and Machine Learning

A Dissertation

Submitted to the Faculty

of

Drexel University

by

Samantha Winter

in partial fulfillment of the

requirements for the degree

of

Doctor of Philosophy

April 2017

Acknowledgements

This dissertation would not have been possible without the support of Michael Lowe, my graduate advisor and mentor. I am so grateful for his mentorship, not only on this project, but also throughout graduate school. He serves as a model for hard work and integrity, traits that I hope to emulate throughout my career. I am so thankful for the time, resources, ideas and enthusiasm he has devoted to my research and to me personally. Without his guidance and support, so many of my successes would not have been possible.

I would also like to thank my committee members, Karol Osipowicz, Zoe Zhang, Nancy Lee, Sonja Yokum and Anna Rose Childress for helping me imagine, work through and ultimately complete this complex and novel project. Specifically, I'd like to thank Eric Stice and Sonja Yokum for their hard work and extreme generosity in collecting and sharing this wonderful dataset with me. Many thanks to Zoe Zhang for her patience in teaching me a great deal about these techniques and for sharing her scripts and expertise with me. Thanks to Karol Osipowicz for being my neuroimaging guru throughout this project and graduate school, and for regularly treating my neuroses with a good dose of humor.

In addition, I would like to thank to the adolescents and their families who participated in the study and were so willing to share their time to benefit our understanding of obesity proneness.

Finally, I want to express a huge thanks to my mom, dad, and brother Maury who have been a source of unending support to me throughout my doctoral

training and my life. A special thanks to Alex, who inspires me every day to challenge myself to be a better me. I am so grateful for their support, love and enthusiasm for every one of my endeavors. Nothing I do would be possible without them.

Table of Contents

List of Tables

LIST OF FIGURES

Abstract

Predicting Weight-Related Outcomes in Healthy Adolescents: Clinical Applications of fMRI and Machine Learning

Samantha R. Winter

Obesity and obesity-related diseases have increased dramatically worldwide in recent years; however, previous studies have shown that weight loss interventions are largely ineffective in the long term. As a result, focus has shifted to determining objective predictors of weight gain, including neural correlates of such weight behaviors. Previous imaging studies have investigated the brain using univariate methods that do not enable detection of the multivariate complex patterns that may separate those prone to weight gain from those who are not. The present study used a supervised machine learning method (SVM; support vector machine) to classify adolescents (N = 135) into those who would gain weight or become weight variable over a 3-year period. Whole brain SVM analyses were performed for a) structural MRI, b) fMRI during milkshake tasting, c) fMRI during an inhibitory control go/no-go task, d) fMRI during a food image task and e) a combination of modalities. Structural scans did not significantly predict weight gain or weight variability. For functional scans in the milkshake and food image paradigms, SVMs significantly predicted weight gain using a linear mixed-effects method. Predictive accuracy increased when these two paradigms were concatenated in a single model. SVMs did not reach significance for classification of weight variability in any of the paradigms. These results support that weight

gain proneness can be characterized by different neural activation to food stimuli and that these differences precede weight gain. The findings suggest that SVM may be useful for identifying neural markers of weight gain proneness.

Chapter 1: Overview

According to recent estimates, 69% of Americans are either overweight or obese (Flegal, Carroll, Kit, & Ogden, 2012), with rates continuing to rise, especially among adolescents (Ogden et al., 2016). Overweight and obesity are associated with a number of conditions and comorbidities that threaten health, wellbeing and longevity (Field et al., 2001). In addition to health consequences, obesity and related illnesses cost the United States an estimated $190 billion per year (Cawley & Meyerhoefer, 2012). Weight variability, or fluctuations in weight independent of weight trajectory, is a less explored construct than overweight or obesity, but has been linked to subsequent weight gain (Michael R Lowe, Feig, Winter, & Stice, 2015) and poor health outcomes, such as diabetes and cardiovascular events (Folsom, French, Zheng, Baxter, & Jeffery, 1996).

Despite staggering costs and fifty years of effort, little has been done to stop or reverse the obesity epidemic. Interventions that have been developed are often successful in the short term, but nearly all weight that is lost is regained (Kramer, Jeffery, Forster, & Snell, 1988; MacLean, Bergouignan, Cornier, & Jackman, 2011). Even among those few who are successful in maintaining weight loss, it appears that interventions focusing on weight loss do not reduce the rates of cardiovascular events or concerns (Johnston, Moreno, & Foreyt, 2014; Poirier et al., 2006). As a result, a great deal of focus has shifted from intervention toward attempts to understand the etiology and work toward prevention of overweight or obesity. However, in order for prevention techniques to be most effective and least cost prohibitive, such efforts should be aimed at understanding who is at risk

for development of weight gain and weight variability in order to provide targeted efforts to those who are most likely to benefit from them.

Predictors of development of future weight gain and weight variability can be examined from a number of perspectives – including (but not limited to) biological, physiological, neurological, psychological, behavioral and sociocultural. Studying neurological patterns in relation to future weight outcomes is particularly promising, as the brain is a hub for all potential levels of analysis – it drives and/or mediates behavior, appetite-related hormones, psychological approaches to food intake, and autonomic physiological responses to stimuli. Additionally, neurological evidence provides a means of objectively quantifying differences between individuals. The overarching purpose of the current study is examine how structural and functional brain patterns may be used to accurately predict who will go on to a) gain weight and b) exhibit greater weight variability. It is the hope that these findings will provide a more thorough etiological understanding of weight and weight disorders as well as inform future targeted prevention efforts.

Specific Objectives

The broad aim of the current study is to examine the viability of using brain-based measures to accurately classify individuals into future weight change phenotypes. Prior literature has focused on localization of brain regions that predict weight gain (Stice, Burger, & Yokum, 2015; Stice, Yokum, Burger, Epstein, & Small, 2011; Sonja Yokum, Gearhardt, Harris, Brownell, & Stice, 2014). The current study extends these findings by using an existing dataset to

determine if a data-driven model utilizing the same paradigms can be used to accurately categorize individuals into a specific "proneness" group. Specifically, we aim to examine if:

a) Structural and functional brain measures can predict whether an individual will gain weight from baseline to 3-year follow-up using a multivariate approach.

b) Structural and functional brain measures can predict an individuals' weight variability status from baseline to 3-year follow-up using a multivariate approach.

Clinical Utility of this Study

We developed this study with two primary goals. First, the study was constructed to apply a novel data-driven method to identify brain regions useful for the prediction of weight gain and weight variability. The constellation of predictive factors considered in the current study has been examined in other literature (Stice et al., 2015; Stice, Yokum, Bohon, Marti, & Smolen, 2010; Stice et al., 2011), but never in this manner. This study proposes to take a data-driven, post-hoc approach to better understand the data that is already collected, rather than taking the traditional a-priori hypothesis-driven approach. More information on this method is discussed below. Second, the study aims to provide preliminary data on the efficacy of applying machine learning and classification techniques for the purposes of eating-related clinical outcomes.

Chapter 2: Introduction

Overview of Overweight/Obesity

Obesity is among the most expensive and important public health issues worldwide. Overweight and obesity are most often measured by body mass index (BMI), which is calculated by weight in kilograms divided by height in meters squared (Garrouste-Orgeas et al., 2004). In adults, overweight is a BMI between 25 and 29.9 kg/m^2 and obesity is a BMI greater than or equal to 30 kg/m^2. A recent study using NHANES data from 2009-2010 reported a combined rate of overweight and obesity at 69.2%, with obesity alone rates of 35.9% (Flegal et al., 2012). A study of overweight and obesity rates among children and adolescents in the same year (2009-2010) reported a combined overweight and obesity rate of 31.8% and obesity alone rates of 16.9%, with somewhat higher obesity rates in adolescents than in children (Ogden, Carroll, Kit, & Flegal, 2012; Ogden et al., 2016) The fact that children and adolescents show a reduced rate of overweight and obesity compared to the adult population suggest them to be a viable target for preventative efforts.

Overweight and obesity are directly caused by the maintenance of a positive energy balance, a state in which energy intake exceeds expenditure (Blundell & King, 1996). Overconsumption is promoted by an environment replete with food cues, resulting in an obesogenic environment that drives individuals toward food for hedonic as well as homeostatic reasons (Blundell & King, 1996). This environment is thought to interact with biological processes, such as genetic

expression and hormone production/circulation, which only contributes to difficulties in maintaining weight loss and avoiding weight gain (Trayhurn, 2005).

In order to best manage the obesity epidemic and the ever-growing obesogenic environment, prevention of weight gain is essential. Environment and behavioral modification programs intended to induce weight loss are often successful in the short term, with participants often losing 7-10% of their original body weight at 6 to 12 month follow-up, however, the majority of them regain all lost weight within 5-years (Jeffery et al., 2000; Jeffery et al., 2009; Sarwer, von Sydow Green, Vetter, & Wadden, 2009; Turk et al., 2009; Wing, Crane, Thomas, Kumar, & Weinberg, 2010). Furthermore, research has suggested that once an individual is obese, weight loss may not be able to wholly reverse the increases in cardiovascular and diabetes risk (Group, 2014). From a biological perspective, mechanisms intended to regulate energy balance and metabolic rate evolved with the primary purpose of preventing starvation in the case of food shortage (Brown, 1991). These mechanisms effectively compensate for energy scarcity through biological compensation and store excess intake for a potential lack of availability. As a result, this system supported survival in times when food was scarce, but now inherently promotes weight gain in an obesogenic environment replete with food and food cues. Converging lines of evidence show that once individuals lose weight, their body will mount multiple defenses in order to aid in returning to their higher weight, which has now become their "set point" (Ferrannini, Rosenbaum, & Leibel, 2014; Halaas et al., 1997). Additionally, as the

rate of overweight and obesity are so high, the economic burden of providing treatment to these individuals would be overwhelming.

It is both difficult and expensive to treat individuals after they have become overweight or obese. Thus, prevention of future weight gain is a crucial element in management of the obesity epidemic. However, in order to provide efficient and effective prevention programs, it is important to learn who is most predisposed to development of obesity in order to target these programs toward those who need them most. To that end, individual predictors of future weight gain have been identified in the literature. However, few reliable predictors exist and they only account for a small amount of the variance in observed weight gain. Thus, a novel multivariate and objective approach that highlights patterns in already existing data may help to create a more reliable profile of weight gain proneness. Rather than making educated guesses about what variables might predict weight gain a priori, the approach proposed here will identify predictors of weight gain based on a longitudinal examination of which participants actually gain the most weight.

Overview of Weight Variability

Weight variability, unlike weight gain and overweight/obesity, is a newer construct and not abundantly represented in the literature. Historically, the term 'weight variability' was used synonymously with 'weight cycling' and represented either self-reported or objective fluctuations in weight over a circumscribed period of time (Heatherton, Polivy, & Herman, 1991; Lissner et al., 1991). In these studies, weight cycling involved intentional weight losses

followed by subsequent weight gains. These studies commonly calculated weight cycling scores as the sum of the absolute values of the difference in weight from one observation to the next (Heatherton et al., 1991) or by counting the number of times in which individuals had lost and regained a circumscribed amount of weight within a given period of time (Mason et al., 2013; Stevens et al., 2015). In using these methods, weight gain and weight variability are inherently confounded, as neither method controls for the overall trajectory of the weight change or the magnitude of net weight gain. Additionally, this construct was mostly examined in already overweight or obese individuals who are engaging in volitional inhibition in attempts to lose weight.

Weight variability as it is defined in the recent literature was, in contrast, derived from the study of normal weight individuals rather than those who are already overweight or obese. These studies have calculated weight variability using a root mean squared error (RMSE) method (Folsom et al., 1996; Michael R Lowe et al., 2015), which represents the variation around the slope of weight change over time for each individual. This method picks up on individual differences, weight gains and losses regardless of the source of these changes. Although weight variability is expected to be at least somewhat correlated with weight change, weight variability may pick up on subtle weight fluctuations that net weight change analyses obscure.

Body weight in healthy animals and humans is typically regulated in an unconscious manner (Barsh, Farooqi, & O'Rahilly, 2000). Over the course of a single year, energy intake and expenditure (termed energy flux) in an average

individual is approximately 700,000 Kilocalories (Keesey & Hirvonen, 1997). Despite the enormous amount of energy flux, historically humans maintained a relatively stable body weight. This weight stability likely represents an intact and well-toned homeostatic system that counterbalances both upward and downward deflections in energy balance with regulatory metabolic, hormonal and behavioral responses. Recent studies have found that increases in the level of weight variability are linked to subsequent weight gain (Michael R Lowe et al., 2015). It is possible that greater than average variability in body weight represents a disruption in the homeostatic system that was once able to effectively sense and respond to upward and downward energy balance changes. If this theory is true, it is possible that the same underlying process that produces net weight gain is *first* reflected by an increased level of weight variability. That is, increased level of weight variability may be an early marker of weight gain proneness that precedes a long-lasting susceptibility to weight gain.

As stated above, greater weight variability has been predictive of future weight gain (Michael R Lowe et al., 2015), suggesting that weight variability may predate increases in weight level and ultimately result in development of overweight and/or obesity. In earlier literature, weight cycling (intentional weight loss followed by gains) has been linked to poor cardiovascular outcomes and strokes in a number of studies. This effect persists above and beyond the contribution of average body weight or weight gain (Diaz, Mainous, & Everett, 2005; Folsom et al., 1996; French et al., 1997; Lissner et al., 1991). Researchers hypothesize that the negative impact of weight cycling is a byproduct of the stress

that repeated weight losses and gains places on the body and biological systems regulating weight (Lissner et al., 1991). Although weight variability as it is defined in the current proposal is not the same as weight cycling, the relation of both of these constructs to relevant outcomes suggests weight variability to be a concept warranting further exploration.

Predictors of Weight Gain and Weight Variability

Identifying the predictors of weight gain and weight variability is crucial in developing effective targeted interventions and preventative care. Predictors inform *who* is most vulnerable and in some cases, *what* should be targeted, and *why* they are susceptible. Although a number of discrete predictors of weight gain have been identified, they vary in their degree of predictive efficacy and to date there is still no holistic understanding of individual differences in weight gain proneness.

Behaviorally, numerous variables have been predictive of subsequent weight gain in prospective studies. Proximal and strong predictors of subsequent weight gain in studies of adolescents include greater dietary fat intake (Maffeis, 2000), higher total caloric intake (Berkey et al., 2000; Butte et al., 2007), lower basal metabolic rate (Butte et al., 2007) and decreased physical activity (Butte et al., 2007). More distal candidate predictors include a history of dieting behavior in adolescents and young adults (M. R. Lowe, Annunziato, R.A., Markowitz, J.T., Didie, E., Bellace, D.L., Riddell, L., Maille, C., McKinney, S., Stice, E., 2006; Michael R. Lowe, Doshi, Katterman, & Feig, 2013), elevated weight in childhood (Must & Strauss, 1999), parental obesity (Salbe, Weyer, Lindsay, Ravussin, &

Tataranni, 2002; Whitaker, Wright, Pepe, Seidel, & Dietz, 1997), impaired inhibitory control in children, adolescents and adults (assessed using both self-report and behavioral inhibition tasks) (Francis & Susman, 2009; Nederkoorn, Houben, Hofmann, Roefs, & Jansen, 2010), increased reward sensitivity among young adults (C. Davis, Patte, K., Levitan, R., Reid, C., Tweed, S., & Curtis, C., 2007) and impaired delay discounting in children, adolescents and adults (Appelhans, 2012; Francis & Susman, 2009).

Environmental factors also play a role in predicting weight gain and obesity onset among adolescents, with close proximity to fast food establishments and lack of access to organized activities/sports conferring elevated risk for subsequent weight gain in adult and adolescent participants (Francis, Lee, & Birch, 2003; Papas, 2007). Popular entertainment and most jobs in today's society have also promoted a more sedentary lifestyle that is ingrained at a young age (Mozaffarian, Hao, Rimm, Willett, & Hu, 2011). This lifestyle directly results in decreased energy expenditure, which contributes to increases in weight level. Although some individuals appear to be resistant to this environment and remain in a healthy weight range, for many the sedentary environment replete with available and unhealthy food options promotes weight gain.

Biological and genetic factors are also linked to development of obesity. Long and short-term regulation of energy intake and expenditure is achieved through communication between the brain and the body's hormonal system (Zheng & Berthoud, 2008). Genome-wide association studies have identified over 50 viable candidate genes that may be linked to obesity. However, research on these genes

suggests that genetic variants and mutations account for only a small percent of the variance in weight (Speakman et al., 2011). One specific twin study suggests that most genetic factors only explain a few hundred grams of body weight for each genetically predisposing allele (Hebebrand & Hinney, 2009). One exception, mutations in the melanocortin 4 receptor, accounts for 5% of morbidly obese patients (Wangensteen, Undlien, Tonstad, & Retterstøl, 2005). Animal and human studies have also identified certain viruses that may be involved in the cause of obesity, including adenovirus infection (Dhurandhar, Kulkarni, Ajinkya, Sherikar, & Atkinson, 1997; van Ginneken, Sitnyakowsky, & Jeffery, 2009). Most likely, the environment influences biology (gene expression, hormonal signaling and/or infection contraction), which ultimately results in weight gain (Ravussin & Bogardus, 2000).

Causes of weight variability remain largely unknown. One hypothesis is that weight variability is a byproduct of an ambivalent relationship with food in which appetitive drive toward food is coupled with a desire to restrict intake, resulting in a pattern of gains and losses (Keller & Siegrist, 2015). However, it is also possible that increased weight variability is not volitional and is an indication of deteriorating homeostatic control that previously closely regulated food intake. Another possibility is that some individuals are inherently susceptible to greater levels of weight variability than others.

It is clear that we have only scratched the surface in identifying predictors of weight gain and weight variability. There is a great deal more to be considered in order to accurately predict *who* is most vulnerable to weight gain and weight

variability and *why* that vulnerability exists. Neuroimaging methods provide information on which brain regions and brain responses predict these outcomes, which provides strong and objective clues as to *why* certain individuals are more prone than others. Thus, a neuroscience approach adds to the extant literature a more mechanistic explanation of weight gain and weight variability proneness.

Neural Predictors of Weight Gain and Weight Variability

In recent years, a large focus in weight-related research has shifted toward examination of neural correlates and predictors of weight gain and obesity. Neuroscience research may be conducted using a variety of modalities and numerous forms – each best suited for specific research questions. Common forms of imaging analysis include a) examination of brain structure, b) brain function when no explicit task is being performed and c) brain function in response to a specific task. Structural analysis (a) is most commonly used to detect structural anomalies or structural differences between groups. Resting state (b) and functional (c) analyses generally use information about neural activation to analyze theory-driven group trends or differences. In contrast to most traditional methods, the current study uses structural (a) and functional (c) information in a hypothesis-free, data-driven manner to provide sensitive and specific prognostic information about each individual. This method of analysis has been applied to a number of clinical outcomes, but never before to the eating domain.

Below is first a discussion of predictors of weight related outcomes using traditional imaging techniques. This is followed by an introduction to the

technique used in the current study and an example of a clinical finding using this technique.

Structural Magnetic Resonance Imaging

Structural magnetic resonance imaging is the gold standard technique for obtaining 3D images of the brain's structure with high spatial resolution. This non-invasive modality enables examination of individual morphological differences, namely volumetric differences between individuals' gray and white matter structures using a method called voxel-based morphometry (VBM). A growing body of literature is demonstrating the efficacy of markers derived from structural MRI in predicting clinical outcomes and development of treatment protocols. In these studies, regional gray matter volume refers to the volume of functional cells and capillaries whereas white matter volume refers to the volume of myelinated axons routing signals between gray matter regions. Presumably, less gray matter and total brain volume compared to control subjects in these regions correspond to neuronal loss or dysfunction, and thus a reduced capacity to perform tasks involving that region (Yamasue et al., 2003). A number of cross-sectional studies have demonstrated volumetric differences between obese and lean individuals; however, few structural MRI studies have been conducted with the intent of predicting future weight change or weight variability.

In cross-sectional studies it cannot be established whether group differences cause or are an effect of weight status, however these studies constitute the majority of the literature on structural brain differences and weight. Numerous studies suggest that individuals higher in weight have decreased gray matter

volume, particularly in frontal regions (Raji et al., 2010; Willette & Kapogiannis, 2015). In adolescents and adults under the age of 40, the prefrontal cortex emerges consistently as an inverse correlate of adiposity, whereas in older adults, occipital and temporal volume reductions are also consistently observed with increased adiposity (Kennedy, Collins, & Luciana, 2016; Willette & Kapogiannis, 2015). A subset of these studies have also found white matter volume to be inversely related to adiposity, particularly in tracts connecting reward and inhibitory control regions of the brain (Karlsson et al., 2013; Kennedy et al., 2016; S Yokum, Ng, & Stice). Again, in these cross-sectional studies, it is unclear whether structural brain differences precede or are a consequence of weight gain, thus the few prospective studies are discussed below.

A study by Yokum et al (S Yokum et al., 2012) used VBM to examine white and gray matter regions that predict increase in BMI over 1-year follow-up in female adolescents. White matter volume was not related to increased weight level; however, decreases in gray matter volume of the bilateral superior and left middle frontal gyri were related to subsequent weight gain controlling for starting BMI. These regions are largely linked to inhibitory control processes, goal directed behavior and other executive functions. According to the authors, these findings suggest that reduced gray matter volume in these regions result in poor execution of inhibitory control and ultimately weight gain.

Another study examined differences in gray and white matter volume in obesity prone versus obesity resistant adults (Smucny et al., 2012). Obesity prone individuals were defined as normal or overweight, with a first-degree relative with

a history of obesity and as having a history of weight fluctuations. Obesity prone individuals showed reduced gray matter volume in the orbitofrontal cortex (OFC), left insula and cerebellum controlling for BMI. Like the regions observed in Yokum's study, the orbitofrontal region and insula are both thought to be involved in homeostatic regulation, behavioral inhibition and executive function (although the OFC is thought to be more involved in reward processing than other frontal regions) (Bechara, Damasio, & Damasio, 2000; Hare, O'Doherty, Camerer, Schultz, & Rangel, 2008; Menon & Uddin, 2010). The authors similarly suggest that reductions in volume in these regions confer a risk toward poor inhibitory control of food intake. However, this study is limited in that the obesity prone individuals are higher weight than the obesity resistant individuals (although they are all non-obese), because the results may be a byproduct of earlier (pre-study) weight gain, and because objective subsequent weight gain was not measured. An additional prospective study suggests that increases in BMI in older females over a 15-year period predicted an overall reduction in total gray matter volume, but no change in white matter volume (Soreca et al., 2009). However, this study examines females during their menopausal period, so the findings likely differ from what would be expected in an adolescent sample. No studies to date have explicitly examined the relationship between structural volumes in the brain and weight variability.

Functional Magnetic Resonance Imaging

Functional magnetic resonance imaging (fMRI) is a neuroimaging procedure that utilizes MRI technology to indirectly detect changes in brain activity. When a

part of the brain is active and neurons in that region are firing at an increased rate, blood flows to that region to maintain the brains' metabolic demands (Logothetis, 2008). Simply, when a region of the brain is in use, blood flows to that region. The magnetic properties of fMRI permit the detection of a decrease in the deoxygenated blood and thus, localization of brain activity. fMRI most often uses a blood-oxygen-level dependent (BOLD) contrast images or BOLD subtractions, which compare the activation in one brain state to that in another. This process isolates the regions that are active in a specific condition or task, permitting inferences about the functions of specific regions (Logothetis, 2008).

A number of studies have used the BOLD contrast method to isolate regions that predict subsequent weight gain. These studies are diverse in their sample, follow-up time, functional task and specific pre-processing steps used. However, a summary of the studies and the regions that have emerged as significant predictors of future weight gain is discussed below.

The brain's mesolimbic and mesocortical dopamine pathways are thought to be primary reward regions, in which responsiveness may be related to future weight gain. These pathways connect the midbrain (ventral tegmental area) to the ventral striatum (nucleus accumbens) and prefrontal cortices, which facilitates the release and dissemination of the reward neurotransmitter, dopamine (Vucetic & Reyes, 2010). Some theorists argue that it is hyper-responsivity to reward in these regions that confers an elevated risk for weight gain (C. Davis, Strachan, & Berkson, 2004), while others argue that hypo-responsivity of these regions result

in overeating in order to compensate for a reward deficit (Comings & Blum, 2000).

A study by Stice and colleagues potentially reconciles these seemingly contradictory theories. In this study, adolescent girls with and without a specific DRD2 gene polymorphism, which is putatively associated with dopamine signaling in the striatum, were asked to imagine consumption of palatable foods and unpalatable foods shown on a screen. Decreases in mesolimbic and mesocortical reward pathway activation predicted increased weight in those with the polymorphism. Increased activation in the same pathways were linked to increased weight gain in participants without the polymorphism. These findings suggest that these reward circuits are instrumental in predicting weight gain, but that genetic effects moderate the mechanism of action (Stice et al., 2015; Stice, Yokum, Bohon, et al., 2010).

Several other longitudinal studies have implicated these two circuits in the prediction of weight gain; however, specific findings vary from study to study. Greater lateral OFC activation, a frontal cortical region in the mesocortical reward circuit, predicted future increases in BMI in an appetizing food cue attention task in lean to obese adolescent girls (Sonja Yokum, Ng, & Stice, 2011) and in an anticipatory food intake task in lean adolescent girls and boys (Stice et al., 2015). In another study of lean to obese male and female adolescents, greater striatal but not OFC activation in response to food commercials (compared to non-food commercials) predicted increased BMI at 1-year follow-up (Sonja Yokum et al., 2014). Ventral striatum and anterior cingulate activity in response to appetitive

food images similarly predicted weight gain at a shorter 6-month follow up among female college freshmen (Demos, Heatherton, & Kelley, 2012). Taken together, most longitudinal studies support the claim that obesity is associated with hyper-responsivity of reward-encoding regions. However, this effect is likely moderated by genetic influences and specific reward regions implicated differ across study designs.

Studies examining palatable food receipt as a predictor for subsequent weight gain revealed somewhat less consistent findings. Greater activity in the striatum, ventral pallidum and midbrain in response to milkshake receipt predicted weight gain at 1-year follow-up in normal and overweight women, although this study was limited in sample size (Geha, Aschenbrenner, Felsted, O'Malley, & Small, 2013). Using the same paradigm, overweight and obese women who gained weight from baseline to 6-month follow-up showed a reduction in striatal activity compared to their non-weight gaining counterparts (Stice, Yokum, Blum, & Bohon, 2010).

The inconsistent findings of these studies suggest a number of potential interpretations. First, many of these studies are conducted using individuals who are already overweight or obese. Although these studies are longitudinal in nature, this limits the ability to make inferences about initial vulnerability factors for weight gain or obesity onset. Second, these findings suggest large individual differences – in which a certain pattern of activation is a risk factor for some individuals, but not for others. Third, it appears that methodological differences arrive at differing results. Finally, it suggests that normal weight and overweight

individuals' brains respond differently to food cues and differentially predict weight change over time. Evidence suggests that a BMI of around 30 kg/m^2 is the inflection point at which the consequences of significant long-term positive energy balance and/or obesity fundamentally changes brain circuitry and how reward affects weight gain. Specifically, it appears that when an individual is non-obese, their reward response is largely to the taste of food itself, whereas with continued overeating and eventually obesity, the reward response to food is blunted in response to actual food and instead shifts toward anticipation or cues of the food (Stice, Spoor, Ng, & Zald, 2009).

One study to date has examined the relation of brain activity to weight variability, and suggests that a number of brain regions predict future weight variability in in response to milkshake receipt in healthy-weight adolescents from a comparable sample to that used in the current study (Winter, Yokum, Stice, Osipowicz, & Lowe, 2017). Although data suggest that elevated activation of reward and emotion regulation regions in response to milkshake receipt predict future weight variability, these regions (medial PFC, cingulate cortex and insula) are largely non-overlapping with regions predicting weight gain. Similarly, less activation in the precuneus, a self-reference region, predicted lower weight variability at follow-up; this region is also different from those implicated in predicting weight stability or weight loss in studies examining net weight change as an outcome of interest.

Although the weight variability and imaging literature is still in its infancy, findings suggest that neural regions predicting weight variability are at most

entirely orthogonal or at least qualitatively different from those predicting future weight gain. This bolsters the assertion that a combination of weight gain and weight variability may provide a more holistic picture of weight phenotype. The inconsistent findings across all the aforementioned fMRI studies also underscore the need to examine normal weight individuals in an attempt to disentangle discrete predisposing factors from consequences of weight gain and/or weight variability. These findings finally suggest the potential efficacy of examining individual-level differences in the brain using data-driven methods that may capture subtle structural and functional brain patterns that the conventional group-level analyses obscure.

Introduction to Machine Learning in MRI

Machine learning models were first employed in computer science in an attempt to allow computers to learn without being explicitly programmed. Since their inception, machine learning analyses have been applied to numerous other domains, including psychology and neuroscience. In recent years, there has been increased interest in using machine learning classifiers for analyzing patterns within structural and functional MRI data (Pereira, Mitchell, & Botvinick, 2009). Traditional neuroimaging methods use a general linear model (GLM) to predict a time series of voxels based on an experiment's design. Machine learning classifiers, in contrast, are used in the opposite direction and predict parts of the experiments' design from the voxels themselves (Pereira et al., 2009). This means that rather than examining a correlation between a behavioral outcome and a series of voxels, the brain is iteratively examined to find the maximally

discriminating brain regions between two groups. This classifier is then able to predict to which group a brain belongs based on the patterns of the voxels themselves.

Machine learning models differ from traditional GLM-based fMRI analysis techniques in a number of important ways. First, in traditional GLMs, the outcomes are based on a number of mean responses. For example, the mean response to two different experimental conditions may be averaged and then contrasted to determine an average mean difference in neural response between those two conditions. Therefore, the presence of significant results is largely reliant on the strength of the manipulation or magnitude of the difference between conditions. Machine learning models, in contrast, are powerful in that they are sensitive to discriminating group differences without a strong contrast, provided the differences exist (T. Davis et al., 2014). Second, univariate (or GLM) analyses relate psychological or physical dimensions to single voxel activation and as a result, may fail to encapsulate patterns that have a distributed and multidimensional effect on activation. Machine learning (or multivariate pattern analysis; MVPA) models are more sensitive to information from multiple voxels at once, providing a richer code for a particular psychological or physical construct (T. Davis et al., 2014). Finally, machine learning models are evaluated for their predictive accuracy, which allows novel information (in this case, brains) to be evaluated and assigned a predicted outcome. This adds a practical prognostic component to traditional univariate analyses and can also aid in determining the efficacy of specific tasks in contributing to accurate classification

to a specific outcome of interest (Kaplan & Meyer, 2012; Zhang, Yaseen, Galynker, Hirsch, & Winston, 2011).

Machine learning models can take on numerous forms and may be used to answer an array of research questions. The most data-driven methods are considered "unsupervised" machine learning models that derive patterns from the data themselves, without using any behavioral or other information for guidance. The method employed in this study is "supervised", meaning the outcome groups are pre-specified (for example, high weight gainers or low weight gainers) and patterns are iteratively examined in order to determine which activation patterns produce a maximal separation between groups. Functionally, the machine learning classifier takes as an input a set of examples for "training" where a class label (i.e. "high weight gainer" or "low weight gainer") is associated with each example. Training refers to the period in which data is continuously fed into the classifier, and the discriminant ability is refined with each new example to create a maximally discriminant algorithm. Following training, a new set of examples will be provided and the classifier will output a class label belonging to the discrete set of pre-specified categories. This process, called "testing", evaluates if the classifier has learned enough about the groups to predict classes of completely novel examples. Following the testing phase, the classifier will be evaluated for accuracy – how often it classified examples into their correct categories.

In a machine learning classifier-based analysis, there are a number of decisions about the data that must be made. A summary of the decision points that were necessary is presented below, followed by an illustrative example utilizing a

similar design to the proposed study and finally followed by the methods for the current study. The first decision necessary is the type of classifier desired. There are numerous classification training methods – each suited for specific datasets and specific research questions. Popular classifier categories include Naïve Bayes classifiers, Logistic Regressions, Decision Trees and Support Vector Machines. Although each classifier has advantages and disadvantages, the most common classifier training method observed in MRI and fMRI studies is the linear Support Vector Machine (SVM) and this method was used in the present study (Pereira et al., 2009). This method is best suited and superior to other classifiers when there are dichotomous discrete outcome variables, high dimensional spaces, and a large number of correlated features. This classifier technique iteratively seeks to discover a subspace with the largest margin ("hyperplane") separating examples from the two classes (Bishop, 2006). Figure 1 illustrates this concept in a theoretical 2-voxel brain. In this example, each class label is given a value of either -1 or +1. The hyperplane is a separation plane that is constructed to represent the location in which the training samples of the two classes differ most (Wang, Childress, Wang, & Detre, 2007). In essence, the hyperplane separates the two groups in order to determine the maximally differentiating characteristics to facilitate the most accurate classification of an unfamiliar example.

Following classifier choice and prior to actually training the SVM or applying the classifier, the MRI or fMRI data needs to be transformed into a set of examples. This required making three decisions about the data: 1) what components of the data should be used as features, 2) how to extract the relevant values from the data

to create those features, and 3) what outcome is being predicted. The examples may be the participants themselves. In structural MRI, the features may be volumes of a specified set of brain regions for each participant. Together, each example has a series of features that contribute to the prediction of their class. In fMRI data, features may be comprised of a number of possible options. Features may be each individual voxel from each TR within a specific trial-type, may be each voxel in the average of several TRs of a trial type or each voxel's ß-weight from a contrast map capturing the difference in activation between two trial types. In making this decision, one must consider the tradeoff between having numerous noisy examples or few clean examples. Having more examples will result in better estimates of the parameters, but only provided that there is a large enough signal to noise ratio that the classifier can magnify the signal and eliminate the noise (Pereira et al., 2009).

Because the features are most often voxels in MRI and fMRI, and the features largely outnumber the examples, it is often advantageous to reduce the number of features to a more manageable number. This process, termed dimensionality reduction, can apply any of a number of different methods to the dataset. This will yield the same number of examples, but fewer features, only retaining those that are important and useful in the prediction of the outcome.

After completing these steps, decisions must be made as to how to divide the dataset for training and testing. It is possible to train the classifier on half of the data and test on the other half, but this greatly limits the number of examples used for training the classifier, which often will reduce classification accuracy. Another

procedure, cross-validation, will leave single examples out, train the classifier and then test the accuracy. Often, this process will be repeated for each example in the dataset and the accuracy will be computed as the average accuracy across all the examples. This may have a high computational cost if there are a large number of examples. A final alternative, *k*-fold cross-validation, divides the dataset into *k* number of parts. Each group is used as a test-set, with the collapsed remaining groups as the training set. Once each group is used as a testing set, an accuracy score is computed across all the different folds (Pereira et al., 2009).

Once the cross-validation method is selected, the data may be used to train and test the classifier. The results will be evaluated for accuracy of correct classification and a statistical test may be run to determine if the classifier performs significantly better than chance. In MRI and fMRI, a visual representation of pattern localization can be created, presenting the brain maps with those maximally discriminative regions visually represented.

Example of Machine Learning in fMRI

As there have been no food-related machine learning fMRI studies to date, here an illustrative example of a classifier-based study from the mood disorder domain is introduced. The basic aim of the study will be discussed as well as the basic stages of the classifier analysis. The 2009 study by Costafreda and colleagues entitled “Neural correlates of sad faces predict clinical remission to cognitive behavioral therapy in depression” (Costafreda, Khanna, Mourao-Miranda, & Fu, 2009) is discussed in some detail below.

The primary purpose of this study was to identify neural patterns of activity in response to sad faces as a predictive marker of response to cognitive behavioral therapy (CBT) in depressed patients. Of the sixteen participants, nine showed a full clinical response. In this study, each participant was an example, and features consisted of activation level at each voxel for each sad face trial and each non-sad face control trial. This method utilized each trial and thus provided the maximum number of features, maximizing the power of the classifier, but also potentially increasing the noise in the dataset. Standard fMRI preprocessing was completed and principle components analysis (singular value decomposition) was selected as a dimensionality reduction technique. The linear SVM was applied to the lower dimensional basis. The classifier was trained using the leave-one-out cross-validation technique, with data portioned for each cross-validation iteration. Each participant was left out once and an average accuracy across the cross-validation iterations was computed. A binomial distribution was used to evaluate if the classifier performed better than chance.

The classifier had an accuracy rate of 71% (sensitivity) and a specificity rate (true negative rate) of 86% when the faces presented were at their most dissimilar (highest and lowest sadness). Neural regions that identified clinical remission included the anterior cingulate region and a number of other cortical and subcortical regions, including the precuneus, fusiform gyrus and occipital cortex. This suggests that even with a very small sample, machine learning can efficaciously discriminate between groups and perhaps do so with more accuracy because of its data driven approach.

The Current Study

The current study aimed to extend the use of the machine learning and classification techniques to the food domain to determine if such techniques can be used to effectively predict weight gain and weight variability using an existing dataset. Specifically, this study examined the extent to which structural and functional MRI data could be used in a hypothesis-free data-driven manner to draw novel conclusions about a) who will go on to develop certain weight patterns, b) the brain regions predicting these weight patterns, and c) draw tentative conclusions about how the relevant brain regions may explain the behaviors that contribute to the predicted outcomes. To date, much of the food and neuroimaging literature has focused on hypothesis driven regions of interest rather than relying on patterns emerging from the data themselves.

This research has the potential to contribute to and extend the extant literature in a variety of ways. First, this research contributes a classification technique that can be applied to novel adolescent brains to determine with some degree of confidence their proneness to either weight gain and/or weight variability. Second, this research provides some suggestion as to the most predictive metric for these eating behaviors – either structural MRI or one of the three functional tasks included in the present study. Importantly, administering a structural MRI is far less expensive than a functional MRI. If structural MRI can be used to accurately classify individuals' future weight behaviors, this is useful information from a cost-benefit public health perspective. Further, if certain fMRI tasks or certain combinations of fMRI tasks increase the sensitivity of the classifier, this

information is informative in the design of future studies within this population. Third, to our knowledge, this study represents the first attempt to use a data-driven method to isolate brain regions predictive of eating behavior in a prospective design. Brain maps of regions that discriminate between prone and non-prone individuals contribute a more holistic understanding of the brain regions and systems involved in the eventual manifestation of weight gain and weight variability. Finally, this research was intended to introduce machine learning to the eating field in the hope that more data-driven techniques will be applied to better elucidate neural patterns predicting eating-related outcomes.

There are potential limitations of the current study. First, this adolescent sample, while beneficial for early targeted intervention efforts, has a great deal of adaptability and neural plasticity. Therefore, findings from the study may not be applicable to an older population and spatial trends found in this study may not persist over time as the brain matures in these individuals. It is also possible that 4 annual measurements of body weight is not sufficient to truly capture weight variability. However, prior studies have found significant effects related to weight variability measured in this manner, suggesting that even this small number of observations is sufficiently sensitive (Michael R Lowe et al., 2015). It is also possible that while SVM is the most common technique used for multivariate pattern analysis in fMRI, it is too simplistic to capture multivariate patterns in the data. Specifically, if there is a great deal of heterogeneity within one of the groups, a linear classifier with discrete outcome variables may not be appropriate and the classifier will be unable to discriminate accurately between the groups.

These limitations were addressed through robust analyses whenever possible, but must still be recognized in the interpretation of the results from this study.

Chapter 3: Methods

Participants

This dissertation used an already-collected dataset for this novel prospective analysis. A sample of 135 adolescents between the ages of 14 and 17 at baseline were recruited from a city in Oregon via advertisements for a 4-year prospective study. All adolescents were at or near a healthy weight at baseline (deemed by zBMI scores roughly between 27th and 75th percentile). Participants were not eligible to participate if they did not fall within a healthy-weight BMI range, reported current use of psychoactive medications or drugs more than weekly, pregnancy, head injury with a loss of consciousness or current Axis I psychiatric disorder (including anorexia nervosa, bulimia nervosa or binge eating disorder), or were contraindicated for an fMRI scan for any reason. Participants completed fMRI scans at baseline,1-year follow-up, 2-year follow-up and 3-year follow-up, although only baseline scans were examined in the current study. Outcome variables were dichotomized to reduce computational demands and to ease interpretation of both statistical and spatial results of the analyses.

Measures

Table 1. Measures overview

Baseline Characteristics
BMI (Height and Weight measured by stadiometer)
Age (years)
Primary Predictor Variables

Structural MRI	
High-fat/high-sugar + High-fat/Low-sugar Milkshake Receipt > Tasteless Receipt Contrast	
Appetizing > Non-appetizing Food Image Contrast	
Appetizing > Water Image Contrast	
Dessert No-Go > Dessert Go Contrast	
Primary Outcome Variables	
Variable Name	*Description*
Weight Gain (Slope)	Tertile Split
Weight Gain (Simple)	Tertile Split
Weight Variability	Tertile Split

BMI

Height was measured without shoes using a standard stadiometer. Weight was measured without shoes and light indoor clothing using a digital scale. BMI was calculated by dividing the weight in kilograms by the height in meters squared. Research has demonstrated that BMI has suitable convergent validity with measures of body fat using DEXA ($r = 0.80 – 0.90$) and is an adequate alternative for such a metric (Pietrobelli et al., 1998). Furthermore, while age adjusted zBMI was used for recruitment purposes, age unadjusted BMI was used in all analyses

as research has shown that it is more suitable than its age-adjusted counterpart for longitudinal studies (Berkey & Colditz, 2007).

Age

Participants were aged 14 to 17 years old at baseline scan. This age range was selected in order to minimize effects of pubertal development, which has been linked to large BMI changes (Burrows, Díaz, & Muzzo, 2004), while still capturing neural and weight effects during a vulnerable time frame that has been related to outcomes later in life.

Weight Gain

Weight gain was calculated two ways. First, weight gain was calculated using a random slope, linear mixed effects model (LME) using the four measured weights to capture sensitive changes over time, accounting for variability in time between measurements across and within subjects (Stice et al., 2015). Second, weight gain was calculated in a traditional manner using the weight at Year 4 minus the weight at enrollment in order to replicate the most commonly used method in the literature. BMI was used instead of raw weights to minimize the confound of increased height over time in the adolescent sample. After calculation of both weight gain scores, participants were split into thirds. The highest third and lowest third for each of the methods were included in the classification analyses and represent “high gainers” and “non-weight gainers”, respectively. This tertile split was performed in order to obtain greater group separation and maximize discriminative ability.

Weight Variability

Weight variability was calculated using the four measured BMIs in the study, at baseline, 1 year, 2 years, and 3 years, respectively. BMI scores, which reflect body weight adjusted for height, were proposed as opposed to raw weights to ensure that increases in height over time does not confound our analyses. Although the most accurate description of the method is "BMI variability", the term "weight variability" will be used to maintain consistency with the existing literature. Age-adjusted zBMIs were not used as research suggests that within-subject raw-score changes are better to model than removing development related variation with age adjusted scores (Cole, Faith, Pietrobelli, & Heo, 2005). Growth curve analysis was used to calculate BMI change trajectories over these four years. Linear regression curves were modeled taking into account between subject trends in weight over time as well as within subject trends. Following established convention (Michael R Lowe et al., 2015), root mean squared error of variation (RMSE) was calculated around each participant's individual regression line for BMI, provided they had three or more measured weights. Higher RMSE values indicate greater weight variability. Weight variability scores were then split into thirds and the top and bottom thirds were used in the machine learning analyses as "high" and "low" weight variability groups, respectively. Again, the tertile split resulted in a separation between groups that increased the likelihood of meaningful findings. Although it is not desirable to exclude collected data, the substantial sample size allowed this while retaining an acceptable level of power.

Milkshake Paradigm

The current study utilized an adapted version of the original Stice receipt/anticipated receipt milkshake paradigm (Stice, Spoor, Bohon, Veldhuizen, & Small, 2008). This adapted version assesses activation in response to receipt and anticipated receipt of milkshakes that vary in both fat and sugar content and has been used in one study prior to the current one (Stice, Burger, & Yokum, 2013). The milkshakes all used the same non-fat ice cream base, but vary in the type of milk used (whipping cream vs. non-fat milk). Sugar content was manipulated through the presence or absence of sweetened condensed milk. Four milkshakes were used in total: a high-fat, high-sugar milkshake (5.1g fat, 3.4g sugar per fluid ounce); a high-fat, low-sugar milkshake (5.1g fat, 1.7g sugar per fluid ounce); a low-fat, high-sugar milkshake (.5g fat, 4g sugar per fluid ounce); and a low-fat, low-sugar milkshake (.5g fat, 2.4g sugar per fluid ounce). Pilot testing demonstrated that the differences in fat and sugar content were detectable without varying the milkshakes' flavor. The sugar values were not balanced, but were designed so that they had similar energy densities. A tasteless, odorless solution (25 mM KCl, 2.5 mM $NaHCO_3$) was used to mimic saliva as a control contrast. Subjects received the 5 fluids through individual beverage tubes, anchored to the headcoil. This protocol has been used in prior studies (Stice, Marti, Spoor, Presnell, & Shaw, 2008; Stice, Yokum, Bohon, et al., 2010) (Stice et al., 2011) and taste was delivered in the same area of the mouth for each tastant.

Participants were cued with a picture (glass of milkshake or water). All milkshake variants were preceded by the same image of a milkshake to not

confound the neural response to receipt with expectations. During milkshake and tasteless delivery, the cue (1 s) was presented followed by a fixation cross during delivery of the tastant. The delivery of the milkshake and tasteless solution occurred in variable-length blocks (1 block presented 4, 5, or 7 events in each of the 2 runs). An event was considered when a tastant was delivered (0.7 cc) over 5 s followed by 3 s to swallow. Four, 5, or 7 events in a row of the same tastant were considered a block. After a block was completed, subjects received a rinse of the tasteless solution followed by a swallow cue (0.5 s) and a jitter (9–11 s). The tasteless solution followed the same pattern without a rinse. The order of the presentation of blocks (i.e., different tastants) was randomized. Two runs (13 min; 40 s/run) were performed. Each run presented 3 blocks of each of the 4 milkshake types and the tasteless solution in a randomized order. In total, there were 6 blocks (32 events) of each of the 5 tastants presented. Additional explanation of the study parameters can be found in (Stice et al., 2013). For the current study, the high-fat/high-sugar and high-fat/low-sugar milkshakes were contrasted with tasteless, as these were found to activate reward circuitry and produce more robust results than the other conditions in traditional GLM BOLD analyses (Stice et al., 2013).

Food Image Paradigm

This paradigm was designed to examine activation in response to food images of varying palatability (Stice, Yokum, Bohon, et al., 2010). Before the scanning session, participants rated how appetizing they found foods from a set of 100 images. During the paradigm, participants were exposed to the 20 images that

they rated a most appetizing and the 20 images they rated as least appetizing, based on their pre-scan individual ratings. A control image of 20 glasses of water was also included. Stimuli were presented in one run, with each image presented for 5 seconds with a random jitter (2-4 seconds) occurring between images. The participant was asked to imagine tasting and consuming the food or beverage. Total run time was 10 minutes. BOLD response during pictures of appetizing and non-appetizing foods as well as BOLD response during pictures of appetizing foods and water were modeled for classification.

Dessert Go/No-Go Paradigm

A food go/no-go paradigm was employed to assess inhibitory control in response to palatable food images (Batterink, Yokum, & Stice, 2010). This task required subjects to respond to "go" signals, build up a prepotent response, and then occasionally exert inhibitory control in response to "no-go" signals. Participants were presented with images of desserts and vegetables. In one condition, subjects pressed the button when they saw a vegetable, but inhibited their desire to press the button when they saw a dessert. The instructions were then reversed for the other condition. 144 trials were presented in each of the two conditions, with no-go cues preceded by 3, 5 or 7 go cues in order to reduce expectancy effects and thereby increase the commission rate (number of times the no-go signal incorrectly elicits a button press) of no-go trials. Each trial ended with a random 2-4 second jitter during which a fixation cross appeared on the screen. Each run lasted 6 minutes, with a total paradigm time of 12 minutes. BOLD response to no-go dessert trials and go dessert trials were modeled for

classification. Number of commission errors to dessert no-go trials may be modeled as a behavioral metric of failure to inhibit prepotent responses.

Data Acquisition

A Siemens Tim Trio 3T scanner at the Oregon Health & Science University was used to collect all functional and anatomical neural data. Foam padding, a vacuum pillow and tape were used with the intention of limiting motion artifacts. Visual stimuli were presented using a digital projector and reverse screen display system. Participants completed scanning in a single 90-minute session. Head movement for structural and functional scans were monitored using Prospective Acquisition CorrEction (PACE). If head movement exceeded 2mm or 2-degrees change, the operator was notified and re-ran the block. For smaller head movements, PACE adjusts slice position, orientation and re-grids the residual volume-to-volume motion in real time during data acquisition. PACE utilizes techniques of prospective and retrospective motion correction by estimating motion parameters for subsequent volume acquisition based on detecting motion from reconstructed image data.

Structural MRI

A high-resolution inversion recovery T1 weighted 3D brain image was acquired in 8 minutes in a Siemens Tim Trio 3T scanner (MPRAGE, TR/TE of 2100ms/2.4ms, flip angle 15º, TI 1100ms, matrix size 256x256, FOV 22cm, slice thickness 1mm). Images were checked for motion artifacts and if motion exceeded 2mm or 2-degree change during the scan, the operator re-administered the scan. The orientation of the 3D brain volume was identical to functional slices

so that it could be used in conjunction with activation maps to localize function and determine anatomic regions for investigation with the course data for machine learning purposes. See Stice et al., 2013 for additional preprocessing information (Stice et al., 2013).

Functional MRI

Echo planar imaging (EPI) was used to measure BOLD signal. To improve BOLD signal detection and minimize susceptibility-based distortion effects for regions subject to distortion, a high readout bandwidth and shorter echo time was used. A single shot echo planar sequence was used to image the BOLD signal with the following parameters: TR = 2000 ms, TE = 30 ms, flip angle = 80º, in plane resolution of 3.0 x 3.0 mm^2 (64 x 64 matrix; 192 x 192 mm^2 FOV). In order to cover the whole brain, 32 4mm slices (interleaved, no skip) were acquired along the AC-PC transverse oblique plane as determined by the midsagittal section. Slices were interleaved to reduce cross talk of slice selection pulse. At the beginning of each run in the functional scan, MR signal was allowed 12.6 seconds (6 scans) to equilibrate, and will therefore be excluded from analysis.

Data Analysis

Data Preprocessing

Standard preprocessing steps were used for the present analyses and neuroimaging data were preprocessed using SPM12 (Functional Imaging Laboratory, University College of London) by Sonja Yokum and the Oregon Research Institute group in MATLAB (Mathworks, Inc., Natick, MA). Prior to preprocessing, images were realigned manually to the AC-PC line in SPM and

skullstripped using the Brain Extraction Tool in FSL (FMRIB Analysis Group, Oxford, UK). Anatomical data were segmented and normalized using DARTEL, providing a sample-specific template and individual-level deformation fields for use in normalization. Functional data were slice time corrected, adjusted for variation in the magnetic field using field maps, realigned to the mean functional image, coregistered with the anatomical scan and then normalized to MNI using the DARTEL template and deformation fields output. After normalization, data were smoothed using a 6 mm Gaussian FWHM. A 128 second high-pass filter removed low-frequency noise and signal drift. Data were assessed for spikes in mean response and motion outliers using the Artifact Detection Toolbox (ART; Gabrieli Lab, McGovern Institute for Brain Research, Cambridge, MA). Motion parameters were used as regressors in the design matrix at individual level analysis. Image volumes where z-normalized global brain activation exceeds 3 SDs from the mean of the run or shows greater than 2 mm of composite movement were flagged as outliers and removed.

Linear SVM Processing for Structural Scans

For analyses, the feature set for the prediction model contains white and gray matter brain volumes from the 116 AAL-anatomical structures, which were normalized with each subject's intracranial volume to account for head size variation. Structures used can be found in (Tzourio-Mazoyer et al., 2002). Specifically, class labels were either a) high weight gainers OR non-weight gainers, or b) high weight variable OR low weight variable. For this model, examples consisted of each individual participant and each feature was the

volume for any one individual AAL ROI. On the training set, response patterns that maximally discriminate between the outcomes of interest were estimated using information from an algorithm that discarded iteratively the irrelevant volumes (Recursive Feature Elimination; RFE) (Guyon, Weston, Barnhill, & Vapnik, 2002). Hyper-parameters were optimized using a 5-fold nested cross-validation loop using the LibSVM R package. The inner cross-validation was used for choosing the hyper-parameters and the outer cross-validation was used to evaluate the ultimate performance of the model. This means that 5-loop cross-validation was used first to optimize the model on the training data and then test the accuracy of the model using the testing data. The SVM model was trained for binary linear classification. When relevant, a confusion matrix was compiled to demonstrate classification accuracy showing the number of accurate and inaccurate classifications. For all analyses, gender, age and starting BMI were explored as potential moderators and included as covariates when deemed necessary.

Linear SVM Processing for Functional Scans

Processing protocol for functional scans mirrors that which was used in a similar study design by Formisano and colleagues (Formisano, De Martino, Bonte, & Goebel, 2008). For each of the three functional tasks, pre-processed functional time series were broken into trials of interest and beta maps were generated for each participant for each contrast of interest. The beta map for each contrast and each individual was then used as input for the classification to verify the hypotheses that fMRI brain activity discriminates weight gainers from non-

weight gaining individuals and high weight variable from low weight variable individuals. The space formed by the beta-map voxels was used directly as the feature space for classification without a priori ROIs in order to maintain the most data-driven approach possible.

As in the structural scans, multivoxel pattern responses were analyzed using the iterative SVM-based classification algorithm to maximally discriminate individuals who are a) weight gainers OR non-weight gainers, or b) high weight variable OR low weight variable. On the training set, the maximally discriminative patterns were estimated using the iterative algorithm and the test set was used to assess the correctness of classification of unseen examples (participants not used in the training). Non-active voxels were eliminated prior to application of any formal dimensionality reduction technique. In analyses using the R script, active but irrelevant voxels were then iteratively removed using the RFE algorithm within each of the folds in the 5-fold nested cross-validation. Accuracy of the classifier was evaluated by taking the average accuracy across the 5 folds. A confusion matrix was compiled to demonstrate classification accuracy for each task when indicated. Brain maps were also generated for visualization of the pattern differences between labeled groups when appropriate. Significance was assessed using an empirical Monte Carlo permutation test (Mourão-Miranda, Bokde, Born, Hampel, & Stetter, 2005) with 1000 iterations using the parameters described above. The number of times the permutation performance is greater than the observed performance (divided by the number of iterations) represents a *p*-value. All analyses were completed using MATLAB (Pattern Recognition for

Neuroimaging Toolbox; PRoNTo), SPM and R (package LibSVM). Results were obtained in two ways: using PRoNTo and a custom R script that included RFE. There were no significant differences between results, therefore those results obtained using PRoNTo without RFE are reported below.

Chapter 4: Results

Demographics

135 participants were enrolled in the 4-year longitudinal study. Four were excluded because of missing or poorly registered imaging data. After all follow-ups, a total of 111 participants had 4 recorded BMIs and usable imaging data. For specific information about participant flow through the study, see *Figure 2*. Of the 111 participants who completed the whole study, 43% were male (n = 48) and 57% were female (n = 63). Age of participants ranged from 14-16 at enrollment, with a mean age of 14.99 (SD = 0.87). Females (M = 15.15, SD = 0.89) in the study were significantly older than males (M = 14.77, SD = 0.81), $t(111) = 2.36$, $p = 0.02$.

Descriptive Statistics

Information about annual BMIs throughout the study period can be found in *Table 2*. From baseline to 3-year follow-up, 77% of the sample gained weight (n = 85), although only 35% of the total sample gained greater than 10% of the their body mass from baseline to follow-up (n = 39) and 23% (n = 25) were objectively overweight or obese (BMI exceeding 25 kg/m^2) at 3-year follow-up. Of the sample that completed all study visits, 3% identified as Alaskan Native or American Indian (n = 3), 5% as Asian (n = 6), 9% as Black (n = 10), 2% as Native Hawaiian/Pacific Islander (n = 2) and 78% as White (n = 87). Three participants were missing racial information. 8% of the sample identified as Hispanic (n = 9).

Weight gain over the course of the study was calculated using a simple subtraction method (year 3 weight minus baseline weight) and by calculating the slope using a linear mixed effects model. Using the simple weight gain method, weight gain over the course of the study ranged from -2.77 – 19.98 kg/m^2 (BMI units) (M = 1.636, SD = 2.82). Weight gain using the slope method ranged from -0.23 – 3.71 average BMI units per year (M = 0.55, SD = 0.57). Weight variability (measured using root mean squared error) ranged from 0.09 – 6.77 (M = 0.70, SD = 0.69) from baseline to 3-year follow-up. There were no significant differences in these primary outcome variables by gender or age (see *Table 3*). Outcome variables (weight variability, simple weight gain and weight gain by slope) were all significantly correlated with each other, with simple weight gain accounting for 46% of the variance in weight variability ($b = 0.17$, $SE_b = 0.017$, $p < 0.01$, $r = 0.68$), simple weight gain accounting for 91% of the variance in weight gain by slope ($b = 0.19$, $SE_b = 0.01$, $p < 0.01$, $r = 0.95$), and weight variability accounting for 45% of the variance in weight gain by slope ($b = 0.56$, $SE_b = 0.06$, $p < 0.01$, $r = 0.67$).

Following assessment of descriptive statistics, outcome variables were split into tertiles and the upper and lower third of each was retained for subsequent SVM analyses to maximize the discrimination between groups. Grand means and SDs of the retained tertiles for each outcome variable can be found below (see *Table 4)*. Additionally, mean and SD for BMI for each tertile is included in *Table 4* for the weight gain by slope calculation. In the analyses predicting weight gain (either using the simple or slope method), SVMs were modeled with and without

two individuals who lost >10% of their body weight from baseline to follow-up. There were no significant differences with the exclusion of these participants, therefore they are retained in the analyses discussed below. Chi-Square tests of independence revealed that genders were relatively balanced between groups of outcome variables following the tertile split, $p > 0.05$ (see *Table 5)*.

Primary Analyses

For all analyses, a 5-fold cross-validation method was employed using whole brain contrasts (or images) to test classification accuracy. In order to evaluate if a model performed better than chance, Monte Carlo permutation tests ($k = 1000$) were conducted. Sensitivity and specificity (and their corresponding *p*-values) are also provided when either the total accuracy or the class accuracies are significant. When appropriate, brain maps were generated depicting the most relevant brain regions averaging across the folds. Of note, the rankings of brain regions (indicating their importance in the classification algorithm) were similar across all folds, suggesting that the same neural regions emerged across independent folds and are thus reliable within subsets of the sample.

Structural SVMs

Linear SVMs were fit using whole brain images to test classification accuracy to the appropriate group. In the simple weight gain classification analysis, subjects were assigned to the appropriate weight change group in 48% of cases. Classification in this analysis did not perform better than chance, $p = 0.47$. In the weight gain classification analysis using slope, subjects were assigned to the appropriate weight change group in 44% of the trials and did not perform better

than chance, $p = 0.74$. Finally, in the weight variability classification analysis, subjects were assigned to the appropriate group (high or low) in 53% of the trials and did not perform better than chance, $p = 0.29$. See *Table 6* for confusion matrix depicting structural MRI classification accuracy into weight variability groups.

Milkshake Paradigm

Linear SVMs were trained on the ß-weights of the High Fat/High Sugar + High Fat/Low Sugar > Tasteless contrast to test the classification of functional images in the milkshake paradigm. In the simple weight gain classification analysis, subjects were assigned to the appropriate weight gain group (high or non-gainer) in 60.27% of trials (sensitivity 63.89%, specificity 56.76%). Overall classification performed better than chance according to Monte Carlo permutation tests (k = 1000), $p = 0.04$, although neither the sensitivity nor specificity reached statistical significance, $p = 0.08$, $p = 0.34$, respectively. Classification in the weight gain analysis using slope was performed with 63% accuracy (sensitivity 64.86%, specificity 61.11%), which was significantly better than chance, $p = 0.03$ (See *Table 7* for confusion matrix). Again, sensitivity and specificity did not reach significance on their own ($p = 0.09$, $p = 0.13$, respectively); however, it appears that the classification model was better at identifying individuals susceptible to weight gain (sensitivity) than it was at identifying those who were not susceptible to weight gain (specificity). Brain maps for both simple and slope weight gain analyses suggest that the bilateral orbitofrontal cortex (OFC) most effectively discriminated between non-weight gainers and weight gainers. In the weight gain

by slope analysis, the angular gyrus also emerged as an area of effective discrimination. See *Figure 3* for the brain map with the most relevant ß-weights in the prediction of weight gain slope. Linear SVMs were unable to significantly discriminate between low and high weight variability groups in the milkshake paradigm (38.36% total accuracy, $p = 0.99$).

Food Image (Imagine) Paradigm

Linear SVMs were trained on the ß-weights of both the Appetizing > Non-Appetizing food image and the Appetizing > Water image contrasts.

Appetizing > Non-Appetizing. SVMs trained on the Appetizing > Non-Appetizing contrast accurately classified individuals into weight gain groups by slope in 63.01% of trials, with sensitivity of 67.57% and specificity of 58.33%. Overall classification performed significantly better than chance ($p = 0.03$) although neither the sensitivity nor specificity analyses reached significance ($p = 0.07$, $p = 0.19$, respectively; See *Table 8* for confusion matrix). Again, it appears that classification was better for weight gainers than non-weight gainers. Brain maps revealed discriminant activation in the bilateral middle OFC, temporal pole and angular gyrus (See *Figure 4*). Simple weight gain was classified with only 44.44% accuracy ($p = 0.83$). However, when the model was optimized using leave one out per group cross validation (rather than 5-folds), model performance increased to accurate classification in 62% of the trials ($p = 0.09$). Weight variability groups were classified with 54.17% accuracy ($p = 0.22$) and did not perform better than chance.

Appetizing > H20. None of the SVMs trained on the Appetizing > H20 contrast performed better than chance in the classification outcome variables. Overall classification accuracy for weight gain using the slope method was 45.21% ($p = 0.76$); classification accuracy for simple weight gain was 51.39% ($p = 0.47$); classification accuracy for weight variability was 54.17% ($p = 0.33$).

Go/No-Go Paradigm

None of the SVMs trained on the Dessert No-Go > Dessert Go contrasts performed better than chance in the classification of outcome variables. Overall classification accuracy for simple weight gain was 41% ($p = 0.91$). Overall classification accuracy for weight gain using the slope method was 52% ($p = 0.37$). Overall classification accuracy for weight variability was 56.15% ($p = 0.24$). In the weight variability analysis, however, sensitivity was very high and reached significance (70.27%, $p = 0.05$) while specificity was rather low (41.67%, $p = 0.80$). Thus, it appears that linear SVMs in this contrast were accurately able to identify those high in weight variability, but unable to identify those low in weight variability (see *Table 9* for confusion matrix).

Combination of Methods

Because the analyses using the food image task and milkshake task were independently most predictive of weight gain by slope, these modalities were included in a single model to evaluate the predictive accuracy. The SVM trained collectively on Appetizing > Unappetizing, Appetizing > H20 and Milkshake > Tasteless predicted weight gain by slope with 75.34% accuracy ($p < 0.01$). Sensitivity and specificity were both significant with 75.68% of weight gainers

accurately identified ($p = 0.01$) and 75% of non-weight gainers accurately identified ($p = 0.01$). Brain maps again revealed the bilateral medial and lateral OFC and temporal pole to be maximally discriminant between those who gained and did not gain weight from baseline to follow-up (see *Figure 5*). Of note, the OFC and temporal pole were consistently the top weighted brain regions across each of the folds.

Chapter 5: Discussion

The current study sought to establish whether anatomical brain information and/or functional imaging data could predict subsequent weight gain and weight variability. Across the models fitted, it appears that SVMs were not successful in predicting weight variability from baseline to follow-up. In the milkshake and food image paradigms, SVMs successfully predicted weight gain from baseline to follow-up when weight gain was calculated using a mixed-effects linear model (slope). The milkshake paradigm was also used to successfully predict weight gain using a simple subtraction method. The models using the milkshake paradigm to predict weight gain revealed discriminant activation in the OFC and angular gyrus between weight gainers and non-gainers. The models using the food image paradigm to predict weight gain also implicated the OFC and angular gyrus in addition to the temporal pole in discriminating between gainers and non-gainers.

A combined model including the food image and milkshake paradigm successfully predicted weight gain from baseline to follow-up when weight gain was calculated using the mixed-effects model. Like the independent models, this multi-modal model revealed discriminant activation in primarily the bilateral OFC (medial and some lateral) and bilateral temporal pole. The fact that a multi-modal approach had higher predictive accuracy than those using a single imaging task suggests that the food image and milkshake task provide complementary information in the prediction of weight gain. That is, having information from one

task alone may provide some useful information, but together, the predictive power is enhanced considerably.

The neural regions that predict weight gain in this study have been linked to reward processing across a number of domains. A large literature has linked the OFC in particular to reward valuation (in both food and non-food studies), reinforcement learning and hedonic experience (Kringelbach, 2005; Rolls, 2000). Additionally the OFC contains both the secondary taste cortex as well as both secondary and tertiary olfactory cortical regions and is thus critical for encoding the rewarding value of taste and odor (Rolls, 2000). The OFC has also been predictive of future increases in BMI in both an adolescent female sample ranging from lean to obese (Sonja Yokum et al., 2011) and an adolescent lean male and female sample (Stice et al., 2015) using an fMRI regression (GLM) approach. The findings from this study replicate and extend prior literature underscoring the role of the OFC in future weight change. This multivariate classification approach suggests that this region is not only related to reward processing and weight outcomes, but actually is a primary region that *discriminates* between those who will and will not gain weight.

Another region that showed large contribution to the prediction of weight gain in both the milkshake and food image paradigms was the angular gyrus. Activation in the angular gyrus has been inversely related to weight gain (Kishinevsky et al., 2012) and inversely related to viewing of high-calorie food images (Murdaugh, Cox, Cook, & Weller, 2012) in food-related fMRI tasks. The angular gyrus is most often discussed with respect to semantic processing and

language comprehension (Seghier, 2013), but tractology studies have revealed high levels of neural connectivity between this region and diverse other regions including frontal and subcortical reward circuitry (Seghier, 2013). Animal and human studies alike have recognized the angular gyrus in mediating processes ranging from problem solving to attention to future orientation (Göbel, Walsh, & Rushworth, 2001; Grabner et al., 2009). To date, no studies have directly examined or theorized the role that the angular gyrus plays in eating behavior or weight, but it is a region that regularly emerges as a correlate of satiety (Del Parigi et al., 2002) and an inverse correlate of appetitive drive (Batterham et al., 2007). Taken together, it is possible that the angular gyrus is responsible for attentional resource allocation and/or consideration of future goals that is ultimately protective against weight gain. The fact that the angular gyrus emerged as a predictive region in this study suggests that this is a critical region in discriminating weight gain prone from non-weight gain prone individuals.

The temporal pole contributed to the prediction of weight gain, specifically in the food image paradigm. The temporal pole is not considered a reward area, but is rather traditionally implicated in mood regulation and integration of mood with highly processed perceptual information (Mathiak et al., 2011; Olson, Plotzker, & Ezzyat, 2007). That said, connectivity studies in animal and humans alike have suggested that there are reciprocal projections between the OFC and temporal pole, suggesting that this region is at least in communication with reward centers (Cohen, Heller, & Ranganath, 2005; Kahnt, Chang, Park, Heinzle, & Haynes, 2012; Kondo, Saleem, & Price, 2003; Liu et al., 2013). Although the specific role

of the temporal pole remains enigmatic (Olson et al., 2007), it seems to play some role in processes related to primary and secondary reward (Mobbs, Greicius, Abdel-Azim, Menon, & Reiss, 2003; Tanaka et al., 2004). One study (Sonja Yokum et al., 2014) found activation in this region while watching food commercials (compared to a television show) predicted BMI gain in adolescents one year later. More work is necessary to fully elucidate the role of the temporal role in processing of reward, specifically with respect to food, but this study provides preliminary evidence that differential activation in this region may be critical to discriminating those who will gain weight from those who will not.

Taken together, neural regions that emerged in the present SVM analyses overlap with existing literature examining brain regions that correlate with either food reward or subsequent weight gain. These findings both corroborate but also extend that literature by implying that these regions are not only correlated with food-related paradigms, but are actually critical in identifying those susceptible to weight gain. The notion that primarily identical regions (OFC and angular gyrus, specifically) were identified as the strongest discrimination regions in three separate models (food image alone, milkshake alone and combined food image and milkshake) is important for two reasons. First, the replication implies that these regions are truly important in discrimination of weight gain rather than an artifact of a specific task or sub-sample of the data. Second, the replication suggests that these regions are implicated across food tasks that presumably assess different components of food reward. In the milkshake task, the construct assessed was reward *receipt*, where participants were actually tasting a palatable

milkshake; in the food image paradigm, participants viewed pictures of appetizing foods, but did not taste them, thereby the construct assessed was more related to food cue reactivity. These brain regions may be fundamental in the prediction of weight gain across a variety of different task types and modalities.

Interestingly, this novel multivariate classification approach was able to better utilize neural data to predict weight gain than weight variability, and specifically best predicted weight gain calculated by slope. That is, within this normal weight sample, larger differences in neural activation were more related to the average weight change over the four years than simple weight gain. This finding implies that accuracy in the weight gain by slope models was highest because neural patterns are more distinguishable between high and non-weight gaining groups for this outcome than for simple weight gain. There are a number of plausible explanations for this finding. First, given that weight gain by slope and simple weight gain revealed qualitatively similar results, it is possible that indeed the neural patterns are simply more robust for discriminating linear trends in weight gain than simple subtraction from study end to study start. It is also possible, however, that weight gain by slope is merely the "cleanest" manner in which to model inherently messy data. Weight gain through simple subtraction is messy, as it may be picking up on real signal (i.e. trends over time) or may be a product of a randomly selected start and end point of the study without accurately reflecting the trajectory of weight change.

Brain activation was unable to predict weight variability groups within this study. In previous literature brain activation in the milkshake task predicted

weight variability in a different adolescent sample using the traditional GLM method (Winter et al., 2017). Despite these seemingly contradictory findings, weight variability is a construct that is still relatively new to the field and its mechanisms are still poorly understood. It is possible that higher weight variability is not inherently pathological, and a tertile split of weight variability may not be classifying individuals into at-risk and low-risk groups as it was intended. More research is necessary to explore how to best measure, categorize and possibly normalize weight variability data in order to best use it as a clinical tool.

As a result, the current study suggests that among the methods commonly used to conceptualize weight change, weight gain by slope using a linear mixed effects method is the superior method when it comes to discrimination of neural activation. This has implications for the design of future studies in that longitudinal studies may consider using at least annual follow-ups to assess weight a sufficient number of times so that weight gain by slope may be modeled. A number of longitudinal studies still calculate weight gain using a simple subtraction method (Neumark-Sztainer, Wall, Haines, Story, & Eisenberg, 2007) and the current study's finding suggests that using a slope approach in those cases may yield more robust results, especially if prediction of weight gain is among the primary study aims. It is also possible that still better methods of assessing weight behaviors still exist. For example, as some studies have shown neural activation to be more robustly predictive of weight variability than weight gain (Winter et al., 2017), there is perhaps a still unexplored method that could adequately capture

both weight variability and weight trajectory in a single value. Perhaps more thorough exploration of alternative methods for conceptualizing weight will render classification more successful.

Across those analyses that were significant or neared significance, sensitivity was considerably higher than specificity. This indicates that the performance of the models was better at identifying true positives (for example, correctly identifying those who would gain weight) than at identifying true negatives (for example, correctly identifying those who would not gain weight). As the current study is intended to make strides toward identification of those who are prone to weight gain and/or weight variability, it is more important to have high sensitivity than specificity. That is, it is more important to correctly identify those prone to maladaptive weight behaviors than to correctly identify those who are not. From a public health perspective, it is beneficial to identify those who are likely to develop problems even if some individuals are wrongly identified as "prone" – as preventative treatment may be unnecessary but is certainly not harmful to those who are not actually prone.

Despite some promising significant findings, prediction accuracy in the present study did not exceed 75% (65% when only using a single modality). Although in a number of models this classification accuracy was significantly better than chance, a number of subjects were still misclassified; specifically a number of those who did not actually gain weight were misclassified as weight gainers (low specificity). These numbers are not dissimilar from other published studies of between-subject analyses using SVM (Prasanth, Revathi, & Maheswari,

2017). In existing literature, SVMs have been primarily employed as a multivariate classification method within a single subject in order to create a brain discrimination (or discrepancy) map, which delineates between two different experimental brain conditions. With respect to the current study, this may be something akin to discriminating between patterns of activation when tasting milkshake vs. tasting a tasteless solution within a single individual. For illustrative purposes, a supplementary analysis discriminating neural activation between milkshake and tasteless solution receipt was conducted within a randomly selected single subject. In this supplemental analysis, overall classification accuracy of milkshake compared to tasteless trials using the same hyperparameter optimization methods as in the above analyses was 90%. Thus, based on a novel brain input, 90% of trials were correctly identified as being of trial type “milkshake” or trial type “tasteless”. This suggests that there was much higher classification accuracy of the models within a single subject than between a number of subjects. This finding demonstrates the challenges inherent in accurately classifying groups of individuals who are likely heterogeneous in both neural patterns and behavior. The findings from the current study are likely limited by the difficulties in concatenating multi-subject data and attempting to make population-level inferences without being able to account for functional differences between independent subjects. For that reason, while population level findings are preferable from the perspective of clinical utility (and are specifically better suited to ask the question at hand), findings from the current study and prior studies alike suggest that from a computational perspective, machine learning

models will be most accurate when the question of interest may apply to patterns within a single subject.

Limitations in classification accuracy in the current study might also be a byproduct of the sample itself. Although reporting in detail the results of traditional GLMs is outside the scope of this paper, traditional fMRI methods using the same sample to predict the same outcome variables did *not* reveal large significant clusters of brain activation. Based on traditional analyses already conducted on the same dataset, neural activation on the tasks reported above was largely unrelated to both categorical and continuous representations of weight gain and weight variability. Although multivariate approaches such as SVMs are thought to be more sensitive and resistant to between subject variability than GLM approaches (T. Davis et al., 2014), it is possible that there are not gross reliable differences between groups in this sample for any number of reasons, therefore neither traditional nor novel techniques will yield robust results. In this sense, the results from the current study actually may be impressively predictive, as they are revealing at least some reliable prediction accuracy in the absence of robust results using a GLM method. As this study represents the first use of SVM in predicting eating behavior (to our knowledge), it may be worthwhile to examine efficacy in fitting machine learning models to data that are already demonstrated to be predictive of weight gain using traditional models. This approach would demonstrate clearly and interpretably what classification analyses can achieve above and beyond traditional methods, specifically within the eating domain.

That said, the current study does have potential implications for public health and obesity prevention programs. Most behavioral and imaging longitudinal studies that predict weight gain do so significantly, but with relatively low variance explained (e.g. a meta-analysis examining craving as a predictor of weight gain found an overall effect size of 0.33, translating to approximately 11% of variance explain, $R^2 = 0.108$; (Boswell & Kober, 2016). Additionally, these studies have for the most part focused on *what* behavioral factors or neural activation patterns predict weight gain over time, not testing whether these factors are successful in correctly identifying *who* will actually go on to gain weight. Although this seems like a subtle distinction, targeted prevention programs need to identify *who* will go on to gain weight, and thus findings from this study represent potentially viable methods for addressing this issue. Classification accuracy can likely be improved and honed as classification and machine learning metrics are applied more diffusely across other samples and study designs; even among this novel study, however, accurate classification of completely novel brains (with minimal additional information in the model) above levels chance represents an improvement upon prior methods and a viable future direction for research in this field.

Strengths & Limitations

This study had a number of strengths. First, the large sample size with low attrition over the course of the study permitted the power to run novel and exploratory analyses. Second, the study was prospective in nature with a lengthy (3 year) follow-up period. This permitted the prediction of actual weight gain over

time, cover and above developmentally-appropriate weight gain, contributing to the clinical significance of the findings. The study also included a diverse set of imaging paradigms ranging in type and domain of appetitive and self-control probes, permitting assessment across different components of eating behavior. This allowed for inclusion of multiple tasks into a single model and also made possible direct comparison across tasks for insight into which task(s) were most predictive of weight change.

The current study also has several limitations. Although the adolescent age range represents a time of vulnerability toward weight gain, it is also complicated by active, healthy growth. It is possible that some of the adolescents that were categorized as "weight gainers" were actually gaining healthy weight, rather than unhealthy weight. Those in the weight gain group did not weigh significantly less than the non-weight gain group at baseline, so there is no evidence to suggest that they *needed* to gain more weight than their non-weight gaining counterparts, but it is still possible that some of the weight gained throughout the study was of a healthy nature or body mass, rather than body fat. Additionally, the young age group may be a potential reason for lack of findings for the structural images – as structural brain changes likely accumulate with age and experience (Giedd, 2004), so this sample may be too young to examine the full extent of predictive markers.

This study utilized a number of tasks that have been predictive of weight gain in other studies, but preliminary analyses of this dataset did not replicate the robust findings of prior studies using a traditional GLM approach. Thus, it is difficult to evaluate whether or to what extent the novel approach used in the

current study is superior to traditional fMRI analyses. The relatively low classification accuracy may be attributable to difficulties in classification between subjects or may be attributable to non-significant differences between groups within this study. The extent to which either interpretation is true cannot be assessed due to the limitations of this study.

Future Directions

The findings from this study suggest that a) SVMs are able to predict with some accuracy who will gain weight in an adolescent sample, b) brain activation is most successful in classifying weight gainers when weight gain is measured using a slope method, rather than net weight difference, and c) the OFC and temporal poles (and perhaps angular gyrus) are critical regions in differentiating between those who are susceptible to weight gain and those who are not. This study presents early evidence of the viability of a machine learning approach for assessing weight gain proneness between participants, although it may be limited by heterogeneity across subjects. Future work should examine potential moderators that may increase classification accuracy – such as examining males and females separately or considering starting BMI as a covariate. A future study may examine if the predictive ability of weight variability increases with weight gain included as a moderator. Future work should also examine other machine learning methods in order to reveal the best methods for modeling data within this population. Additional work should aim to determine if the findings from this study are replicable in other non-obese populations – such as college students or older adults. Machine learning models may be employed to understand what brain

regions and behaviors are critical in differentiating between other groups within this domain, such as those who will go on to develop eating disorders. As the combination of fMRI and machine learning techniques is still relatively new to the eating domain, future work is necessary in order to better understand what regions are critical in differentiating between groups – in order to both replicate the current findings and extend them to different age groups and populations.

Figure 1. Schematic representation of 2-voxel support vector machine

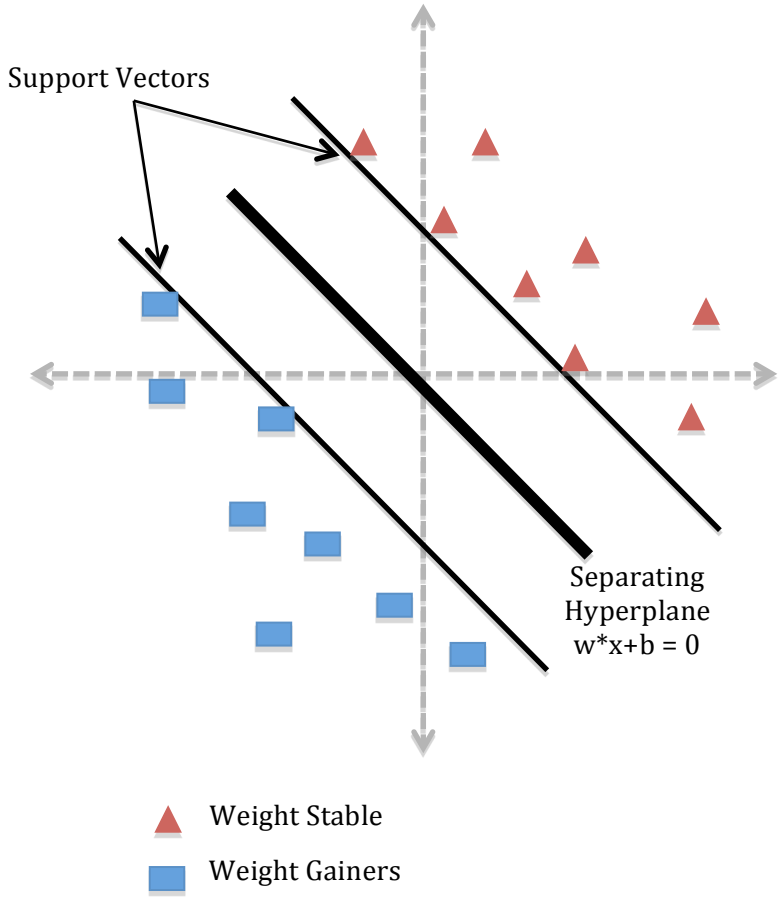

Figure 2. Participant Flow Through Study

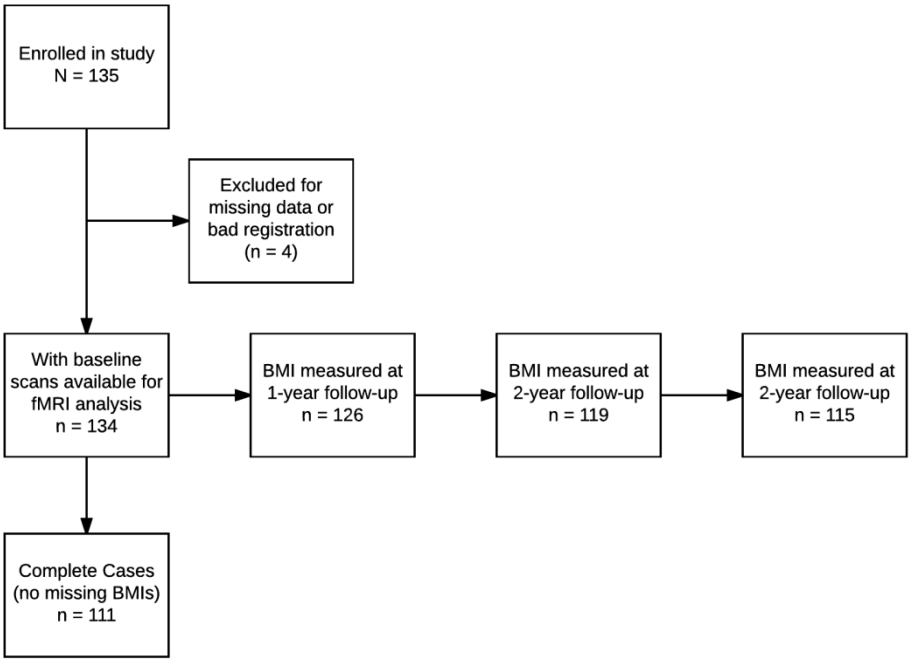

Figure 3. Brain Map of Significant Voxel Patterns for the Prediction of Weight Gain (Slope) in the Milkshake Paradigm

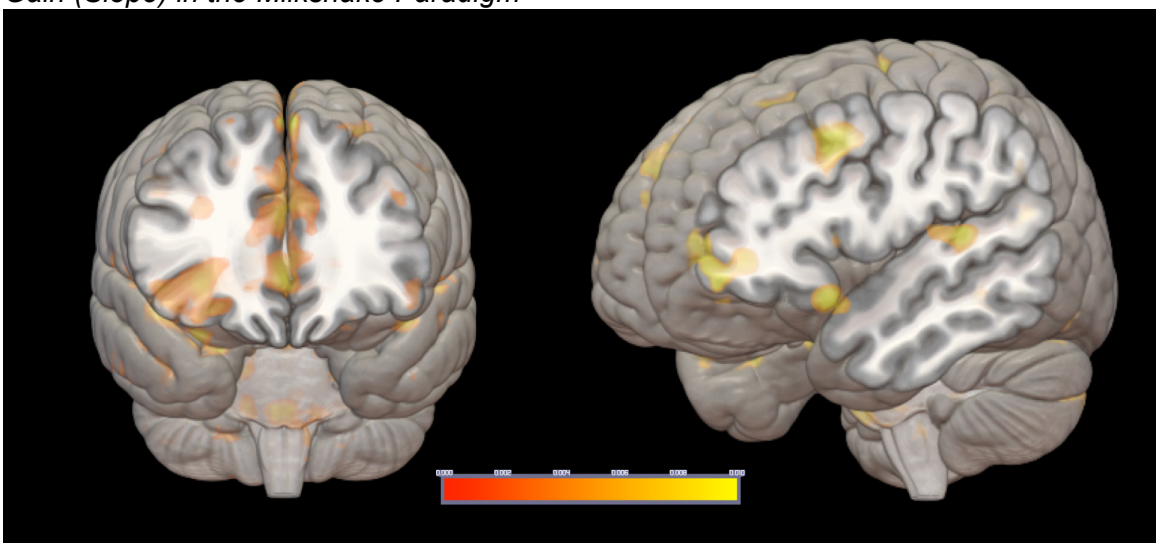

Figure 4. Brain Map of Significant Voxel Pattern for the Prediction of Weight Gain (Slope) in the Food Image (Appetizing > Unappetizing) Paradigm

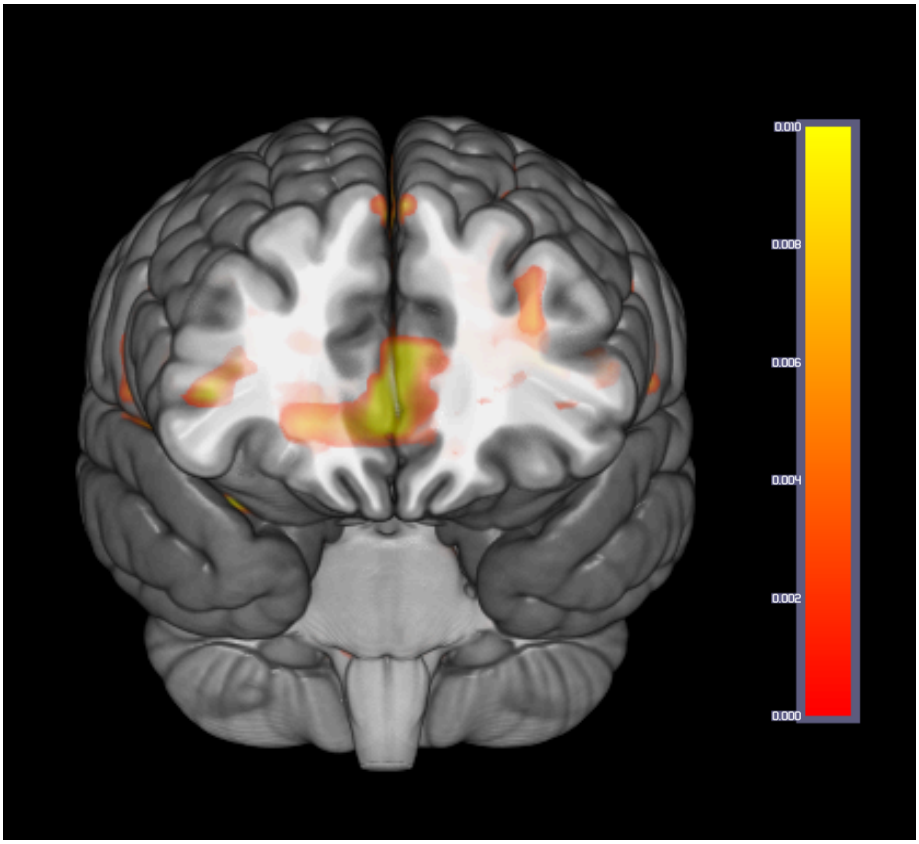

Figure 5. Brain Map of Significant Voxel Pattern for the Prediction of Weight Gain (Slope) in the combined Milkshake and Imagine Paradigms

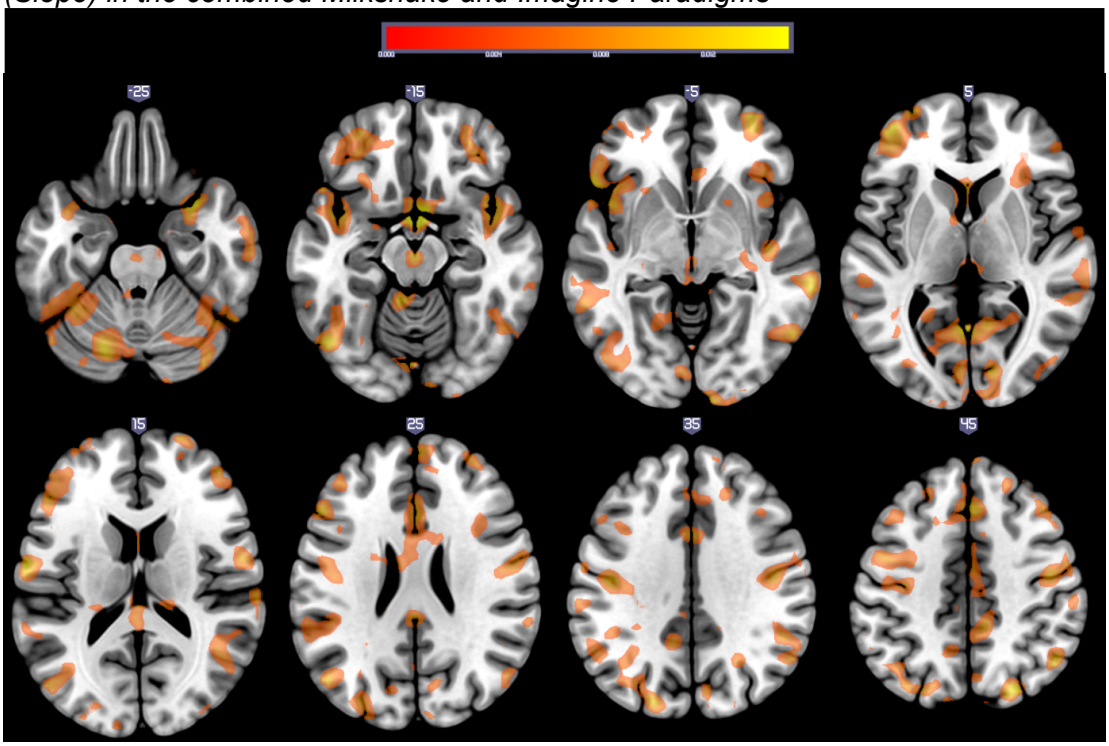

Table 2. BMIs by Year

Year	M	SD
Baseline BMI	21.23	2.31
1 Year Follow-Up	21.55	2.53
2 Year Follow-Up	22.14	2.81
3 Year Follow-Up	22.87	3.6

Table 3. Outcomes of Interest By Gender and Age

Outcome	**Sex**	**N**	**M**	**SD**	**t-test**
Weight Gain by Slope	Male	48	0.569	0.647	t(109) = 0.546, p = 0.586
	Female	63	0.51	0.506	
Simple Weight Gain	Male	48	1.87	3.39	t(109) = 0.93, p = 0.36
	Female	63	1.38	2.23	
Weight Variability	Male	48	0.75	0.97	t(109) = 0.76, p = 0.45
	Female	63	0.65	0.37	

Outcome	**Correlation with Age**
Weight Gain by Slope	r(109) = 0.04, p = 0.64
Simple Weight Gain	r(109) = 0.12, p = 0.21
Weight Variability	r(109) = 0.003, p = 0.97

Table 4. Means and SDs for Low and High Tertiles Retained for Primary Analyses

	Weight Gain (Simple)		**Weight Gain (Slope)**		**Weight Variability**	
	Non	High	Non	High	Low	High
M (SD)	0.65(0.84)	4.41(3.21)	0.06(0.16)	1.13(0.60)	0.31(0.10)	1.20(1.01)

Gain Group (Slope)	***Wave***	***Mean BMI***	***SD BMI***
Non-Gainers	*W1*	*20.21*	*1.95*
	W2	*19.97*	*1.83*
	W3	*19.89*	*1.56*
	W4	*19.88*	*1.65*
Medium-Gainers (not included in SVM)	*W1*	*21.52*	*2.59*
	W2	*21.88*	*2.45*
	W3	*22.40*	*2.21*
	W4	*22.48*	*1.86*
*High-Gainers**	*W1*	*21.98*	*2.02*
	W2	*22.77*	*2.43*
	W3	*21.12*	*2.71**
	W4	*26.16*	*3.55**

**Note: 23 of the 37 participants in the "high weight gain" group were overweight or obese at 3-year follow-up.*

Table 5. Number of Males and Females in Each Outcome Variable Group

	Weight Gain By Slope		
	Low Gain	High Gain	
Sex	(N)	(N)	Total (N)
Male	14	14	28
Female	23	23	46
Total	37	37	74

	Simple Weight Gain		
	Low Gain	High Gain	
Sex	(N)	(N)	Total (N)
Male	15	19	34
Female	22	18	40
Total	37	37	74

	Weight Variability		
Sex	Low Var	High Var	Total
Male	20	15	35
Female	17	22	39
Total	37	37	74

Table 6. Accuracy of Structural SVM in Weight Variability Classification

	High WV	**Low WV**
Predicted High WV	16	15
Predicted Low WV	19	22

Table 7. Accuracy of Milkshake (HF/HS+HF/LS>H20) fMRI Contrast in Weight Gain by Slope Classification.

	High WG	**Non-WG**
Predicted High WG	24	14
Predicted Non-WG	13	22

Table 8. Accuracy of Food Image (Appetizing > Non-Appetizing) fMRI Contrast in Weight Gain By Slope Classification

	High WG	**Non-WG**
Predicted High WG	26	16
Predicted Non-WG	11	20

Table 9. Accuracy of Go/No-Go (Dessert No-Go > Dessert Go) fMRI Contrast in Weight Variability Classification

	High WV	**Low WV**
Predicted High WV	26	21
Predicted Low WV	11	15

References

Appelhans, B.M. (2012). Neurobehavioral inhibition of reward-driven feeding: implications for dieting and obesity. *Obesity, 17*, 640-647.

Barsh, Gregory S, Farooqi, I Sadaf, & O'Rahilly, Stephen. (2000). Genetics of body-weight regulation. *Nature, 404*(6778), 644-651.

Batterham, Rachel L, Rosenthal, J Miranda, Zelaya, Fernando O, Barker, Gareth J, Withers, Dominic J, & Williams, Steven CR. (2007). PYY modulation of cortical and hypothalamic brain areas predicts feeding behaviour in humans. *Nature, 450*(7166), 106-109.

Batterink, Laura, Yokum, Sonja, & Stice, Eric. (2010). Body mass correlates inversely with inhibitory control in response to food among adolescent girls: an fMRI study. *NeuroImage, 52*(4), 1696-1703.

Bechara, Antoine, Damasio, Hanna, & Damasio, Antonio R. (2000). Emotion, decision making and the orbitofrontal cortex. *Cerebral Cortex, 10*(3), 295-307.

Berkey, Catherine S, & Colditz, Graham A. (2007). Adiposity in adolescents: change in actual BMI works better than change in BMI z score for longitudinal studies. *Annals of epidemiology, 17*(1), 44-50.

Berkey, Catherine S, Rockett, Helaine RH, Field, Alison E, Gillman, Matthew W, Frazier, A Lindsay, Camargo, Carlos A, & Colditz, Graham A. (2000). Activity, dietary intake, and weight changes in a longitudinal study of preadolescent and adolescent boys and girls. *Pediatrics, 105*(4), e56-e56.

Bishop, Christopher M. (2006). Pattern recognition. *Machine Learning, 128*.

Blundell, John E, & King, Neil A. (1996). *Overconsumption as a cause of weight gain: behavioural–physiological interactions in the control of food intake (appetite).* Paper presented at the Ciba Foundation Symposium 201-The Origins and Consequences of Obesity.

Boswell, Rebecca G, & Kober, Hedy. (2016). Food cue reactivity and craving predict eating and weight gain: a meta−analytic review. *obesity reviews, 17*(2), 159-177.

Brown, Peter J. (1991). Culture and the evolution of obesity. *Human nature, 2*(1), 31-57.

Burrows, RA, Díaz, N, & Muzzo, S. (2004). [Variations of body mass index (BMI) according to degree of pubertal development]. *Revista medica de Chile, 132*(11), 1363-1368.

Butte, Nancy F, Cai, Guowen, Cole, Shelley A, Wilson, Theresa A, Fisher, Jennifer O, Zakeri, Issa F, . . . Comuzzie, Anthony G. (2007). Metabolic and behavioral predictors of weight gain in Hispanic children: the Viva la Familia Study. *The American journal of clinical nutrition, 85*(6), 1478-1485.

Cawley, John, & Meyerhoefer, Chad. (2012). The medical care costs of obesity: an instrumental variables approach. *Journal of health economics, 31*(1), 219-230.

Cohen, MX, Heller, AS, & Ranganath, Charan. (2005). Functional connectivity with anterior cingulate and orbitofrontal cortices during decision-making. *Cognitive Brain Research, 23*(1), 61-70.

Cole, TJ, Faith, MS, Pietrobelli, A, & Heo, M. (2005). What is the best measure of adiposity change in growing children: BMI, BMI%, BMI z-score or BMI centile? *European journal of clinical nutrition, 59*(3), 419-425.

Comings, David E, & Blum, Kenneth. (2000). Reward deficiency syndrome: genetic aspects of behavioral disorders. *Progress in brain research, 126*, 325-341.

Costafreda, Sergi G, Khanna, Akash, Mourao-Miranda, Janaina, & Fu, Cynthia HY. (2009). Neural correlates of sad faces predict clinical remission to cognitive behavioural therapy in depression. *Neuroreport, 20*(7), 637-641.

Davis, C., Patte, K., Levitan, R., Reid, C., Tweed, S., & Curtis, C. (2007). From motivation to behaviour: A model of reward sensitivity, overeating, and food preferences in the risk profile for obesity. *Appetite, 48*(1), 12-19.

Davis, Caroline, Strachan, Shaelyn, & Berkson, Marni. (2004). Sensitivity to reward: implications for overeating and overweight. *Appetite, 42*(2), 131-138.

Davis, Tyler, LaRocque, Karen F, Mumford, Jeanette A, Norman, Kenneth A, Wagner, Anthony D, & Poldrack, Russell A. (2014). What do differences between multi-voxel and univariate analysis mean? How subject-, voxel-, and trial-level variance impact fMRI analysis. *NeuroImage, 97*, 271-283.

Del Parigi, Angelo, Chen, Kewei, Gautier, Jean-François, Salbe, Arline D, Pratley, Richard E, Ravussin, Eric, . . . Tataranni, P Antonio. (2002). Sex differences in the human brain's response to hunger and satiation. *The American Journal of Clinical Nutrition, 75*(6), 1017-1022.

Demos, Kathryn E, Heatherton, Todd F, & Kelley, William M. (2012). Individual differences in nucleus accumbens activity to food and sexual images predict weight gain and sexual behavior. *The Journal of Neuroscience, 32*(16), 5549-5552.

Dhurandhar, Nikhil V, Kulkarni, Pushpa R, Ajinkya, Sharad M, Sherikar, Abhaya A, & Atkinson, Richard L. (1997). Association of adenovirus infection with human obesity. *Obesity research, 5*(5), 464-469.

Diaz, Vanessa A, Mainous, Arch G, & Everett, Charles J. (2005). The association between weight fluctuation and mortality: results from a population-based cohort study. *Journal of community health, 30*(3), 153-165.

Ferrannini, Ele, Rosenbaum, Michael, & Leibel, Rudolph L. (2014). The threshold shift paradigm of obesity: evidence from surgically induced weight loss. *The American Journal of Clinical Nutrition, 100*(4), 996-1002.

Field, Alison E, Coakley, Eugenie H, Must, Aviva, Spadano, Jennifer L, Laird, Nan, Dietz, William H, . . . Colditz, Graham A. (2001). Impact of overweight on the risk of developing common chronic diseases during a 10-year period. *Archives of internal medicine, 161*(13), 1581-1586.

Flegal, Katherine M, Carroll, Margaret D, Kit, Brian K, & Ogden, Cynthia L. (2012). Prevalence of obesity and trends in the distribution of body mass index among US adults, 1999-2010. *JAMA, 307*(5), 491-497.

Folsom, AR, French, SA, Zheng, W, Baxter, JE, & Jeffery, RW. (1996). Weight variability and mortality: the Iowa Women's Health Study. *International journal of obesity and related metabolic disorders: journal of the International Association for the Study of Obesity, 20*(8), 704-709.

Formisano, Elia, De Martino, Federico, Bonte, Milene, & Goebel, Rainer. (2008). " Who" Is Saying" What"? Brain-Based Decoding of Human Voice and Speech. *Science, 322*(5903), 970-973.

Francis, Lori A, Lee, Yoonna, & Birch, Leann L. (2003). Parental weight status and girls' television viewing, snacking, and body mass indexes. *Obesity research, 11*(1), 143-151.

Francis, Lori A, & Susman, Elizabeth J. (2009). Self-regulation and rapid weight gain in children from age 3 to 12 years. *Archives of pediatrics & adolescent medicine, 163*(4), 297-302.

French, SA, Folsom, AR, Jeffery, RW, Zheng, W, Mink, PJ, & Baxter, JE. (1997). Weight variability and incident disease in older women: the Iowa Women's Health Study. *International Journal of Obesity & Related Metabolic Disorders, 21*(3).

Garrouste-Orgeas, Maité, Troché, Gilles, Azoulay, Elie, Caubel, Antoine, de Lassence, Arnaud, Cheval, Christine, . . . Cohen, Yves. (2004). Body mass index. *Intensive care medicine, 30*(3), 437-443.

Geha, Paul Y, Aschenbrenner, Katja, Felsted, Jennifer, O'Malley, Stephanie S, & Small, Dana M. (2013). Altered hypothalamic response to food in smokers. *The American Journal of Clinical Nutrition, 97*(1), 15-22.

Giedd, Jay N. (2004). Structural magnetic resonance imaging of the adolescent brain. *Annals of the New York Academy of Sciences, 1021*(1), 77-85.

Göbel, Silke, Walsh, Vincent, & Rushworth, Matthew FS. (2001). The mental number line and the human angular gyrus. *NeuroImage, 14*(6), 1278-1289.

Grabner, Roland H, Ansari, Daniel, Koschutnig, Karl, Reishofer, Gernot, Ebner, Franz, & Neuper, Christa. (2009). To retrieve or to calculate? Left angular gyrus mediates the retrieval of arithmetic facts during problem solving. *Neuropsychologia, 47*(2), 604-608.

Group, Look AHEAD Research. (2014). Effect of a long-term behavioural weight loss intervention on nephropathy in overweight or obese adults with type 2 diabetes: a secondary analysis of the Look AHEAD randomised clinical trial. *The Lancet Diabetes & Endocrinology, 2*(10), 801-809.

Guyon, Isabelle, Weston, Jason, Barnhill, Stephen, & Vapnik, Vladimir. (2002). Gene selection for cancer classification using support vector machines. *Machine learning, 46*(1-3), 389-422.

Halaas, Jeffrey L, Boozer, Carol, Blair-West, John, Fidahusein, Naseem, Denton, Derek A, & Friedman, Jeffrey M. (1997). Physiological response to long-term peripheral and central leptin infusion in lean and obese mice. *Proceedings of the National Academy of Sciences, 94*(16), 8878-8883.

Hare, Todd A, O'Doherty, John, Camerer, Colin F, Schultz, Wolfram, & Rangel, Antonio. (2008). Dissociating the role of the orbitofrontal cortex and the striatum in the computation of goal values and prediction errors. *The Journal of Neuroscience, 28*(22), 5623-5630.

Heatherton, Todd F, Polivy, Janet, & Herman, C Peter. (1991). Restraint, weight loss, and variability of body weight. *Journal of Abnormal Psychology, 100*(1), 78.

Hebebrand, Johannes, & Hinney, Anke. (2009). Environmental and genetic risk factors in obesity. *Child and adolescent psychiatric clinics of North America, 18*(1), 83-94.

Jeffery, Robert W, Epstein, Leonard H, Wilson, G Terence, Drewnowski, Adam, Stunkard, Albert J, & Wing, Rena R. (2000). Long-term maintenance of weight loss: current status. *Health psychology, 19*(1S), 5.

Jeffery, Robert W, Levy, Rona L, Langer, Shelby L, Welsh, Ericka M, Flood, Andrew P, Jaeb, Melanie A, . . . Finch, Emily A. (2009). A comparison of maintenance-tailored therapy (MTT) and standard behavior therapy (SBT) for the treatment of obesity. *Preventive medicine, 49*(5), 384-389.

Johnston, Craig A, Moreno, Jennette P, & Foreyt, John P. (2014). Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes. *Current atherosclerosis reports, 16*(12), 1-8.

Kahnt, Thorsten, Chang, Luke J, Park, Soyoung Q, Heinzle, Jakob, & Haynes, John-Dylan. (2012). Connectivity-based parcellation of the human orbitofrontal cortex. *Journal of Neuroscience, 32*(18), 6240-6250.

Kaplan, Jonas T, & Meyer, Kaspar. (2012). Multivariate pattern analysis reveals common neural patterns across individuals during touch observation. *NeuroImage, 60*(1), 204-212.

Karlsson, Henry K, Tuulari, Jetro J, Hirvonen, Jussi, Lepomäki, Virva, Parkkola, Riitta, Hiltunen, Jaana, . . . Salminen, Paulina. (2013). Obesity is associated with white matter atrophy: A combined diffusion tensor imaging and voxel−based morphometric study. *Obesity, 21*(12), 2530-2537.

Keesey, Richard E., & Hirvonen, Matt D. (1997). Body Weight Set-Points: Determination and Adjustment. *The Journal of Nutrition, 127*(9), 1875S-1883S.

Keller, Carmen, & Siegrist, Michael. (2015). Ambivalence toward palatable food and emotional eating predict weight fluctuations. Results of a longitudinal study with four waves. *Appetite, 85*, 138-145.

Kennedy, James T, Collins, Paul F, & Luciana, Monica. (2016). Higher Adolescent Body Mass Index Is Associated with Lower Regional Gray and White Matter Volumes and Lower Levels of Positive Emotionality. *Frontiers in Neuroscience, 10*.

Kishinevsky, Felix I, Cox, James E, Murdaugh, Donna L, Stoeckel, Luke E, Cook, Edwin W, & Weller, Rosalyn E. (2012). fMRI reactivity on a delay discounting task predicts weight gain in obese women. *Appetite, 58*(2), 582-592.

Kondo, Hideki, Saleem, Kadharbatcha S, & Price, Joseph L. (2003). Differential connections of the temporal pole with the orbital and medial prefrontal networks in macaque monkeys. *Journal of Comparative Neurology, 465*(4), 499-523.

Kramer, F Matthew, Jeffery, Robert W, Forster, Jean L, & Snell, Mary Kaye. (1988). Long-term follow-up of behavioral treatment for obesity: patterns of weight regain among men and women. *International Journal of Obesity, 13*(2), 123-136.

Kringelbach, Morten L. (2005). The human orbitofrontal cortex: linking reward to hedonic experience. *Nature Reviews Neuroscience, 6*(9), 691-702.

Lissner, Lauren, Odell, Patricia M, D'Agostino, Ralph B, Stokes III, Joseph, Kreger, Bernard E, Belanger, Albert J, & Brownell, Kelly D. (1991). Variability of body weight and health outcomes in the Framingham population. *New England Journal of Medicine, 324*(26), 1839-1844.

Liu, Huaigui, Qin, Wen, Li, Wei, Fan, Lingzhong, Wang, Jiaojian, Jiang, Tianzi, & Yu, Chunshui. (2013). Connectivity-based parcellation of the human frontal pole with diffusion tensor imaging. *Journal of Neuroscience, 33*(16), 6782-6790.

Logothetis, Nikos K. (2008). What we can do and what we cannot do with fMRI. *Nature, 453*(7197), 869-878.

Lowe, M.R., Annunziato, R.A., Markowitz, J.T., Didie, E., Bellace, D.L., Riddell, L., Maille, C., McKinney, S., Stice, E. (2006). Multiple types of dieting prospectively predict weight gain during the freshman year of college. *Appetite, 47*, 83-90.

Lowe, Michael R, Feig, Emily H, Winter, Samantha R, & Stice, Eric. (2015). Short-term variability in body weight predicts long-term weight gain. *The American Journal of Clinical Nutrition, 102*(5), 995-999.

Lowe, Michael R., Doshi, Sapna D., Katterman, Shawn N., & Feig, Emily H. (2013). Dieting and restrained eating as prospective predictors of weight gain. *Frontiers in Psychology, 4*, 577. doi: 10.3389/fpsyg.2013.00577

MacLean, Paul S, Bergouignan, Audrey, Cornier, Marc-Andre, & Jackman, Matthew R. (2011). Biology's response to dieting: the impetus for weight regain. *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology, 301*(3), R581-R600.

Maffeis, Claudio. (2000). Aetiology of overweight and obesity in children and adolescents. *European journal of pediatrics, 159*(1), S35-S44.

Mason, Caitlin, Foster-Schubert, Karen E, Imayama, Ikuyo, Xiao, Liren, Kong, Angela, Campbell, Kristin L, . . . Ulrich, Cornelia M. (2013). History of weight cycling does not impede future weight loss or metabolic improvements in postmenopausal women. *Metabolism, 62*(1), 127-136.

Mathiak, Krystyna A, Klasen, Martin, Weber, René, Ackermann, Hermann, Shergill, Sukhwinder S, & Mathiak, Klaus. (2011). Reward system and temporal pole contributions to affective evaluation during a first person shooter video game. *BMC neuroscience, 12*(1), 66.

Menon, Vinod, & Uddin, Lucina Q. (2010). Saliency, switching, attention and control: a network model of insula function. *Brain Structure and Function, 214*(5-6), 655-667.

Mobbs, Dean, Greicius, Michael D, Abdel-Azim, Eiman, Menon, Vinod, & Reiss, Allan L. (2003). Humor modulates the mesolimbic reward centers. *Neuron, 40*(5), 1041-1048.

Mourão-Miranda, Janaina, Bokde, Arun LW, Born, Christine, Hampel, Harald, & Stetter, Martin. (2005). Classifying brain states and determining the discriminating activation patterns: support vector machine on functional MRI data. *NeuroImage, 28*(4), 980-995.

Mozaffarian, Dariush, Hao, Tao, Rimm, Eric B, Willett, Walter C, & Hu, Frank B. (2011). Changes in diet and lifestyle and long-term weight gain in women and men. *New England Journal of Medicine, 364*(25), 2392-2404.

Murdaugh, Donna L, Cox, James E, Cook, Edwin W, & Weller, Rosalyn E. (2012). fMRI reactivity to high-calorie food pictures predicts short-and long-term outcome in a weight-loss program. *NeuroImage, 59*(3), 2709-2721.

Must, Aviva, & Strauss, Richard S. (1999). Risks and consequences of childhood and adolescent obesity. *International Journal of Obesity & Related Metabolic Disorders, 23*.

Nederkoorn, Chantal, Houben, Katrijn, Hofmann, Wilhelm, Roefs, Anne, & Jansen, Anita. (2010). Control yourself or just eat what you like? Weight gain over a year is predicted by an interactive effect of response inhibition and implicit preference for snack foods. *Health Psychology, 29*(4), 389.

Neumark-Sztainer, Dianne, Wall, Melanie, Haines, Jess, Story, Mary, & Eisenberg, Marla E. (2007). Why does dieting predict weight gain in adolescents? Findings from project EAT-II: a 5-year longitudinal study. *Journal of the American Dietetic Association, 107*(3), 448-455.

Ogden, Cynthia L, Carroll, Margaret D, Kit, Brian K, & Flegal, Katherine M. (2012). Prevalence of obesity and trends in body mass index among US children and adolescents, 1999-2010. *Jama, 307*(5), 483-490.

Ogden, Cynthia L, Carroll, Margaret D, Lawman, Hannah G, Fryar, Cheryl D, Kruszon-Moran, Deanna, Kit, Brian K, & Flegal, Katherine M. (2016). Trends in Obesity Prevalence Among Children and Adolescents in the United States, 1988-1994 Through 2013-2014. *JAMA, 315*(21), 2292-2299.

Olson, Ingrid R, Plotzker, Alan, & Ezzyat, Youssef. (2007). The enigmatic temporal pole: a review of findings on social and emotional processing. *Brain, 130*(7), 1718-1731.

Papas, M.A., Alberg, A.J., Ewing, R., Helzlsouer, K.J., Gary, T.L., & Klassen, A.C. (2007). The built environment and obesity. *Epidemiologic Reviews, 29*(1), 129-143.

Pereira, Francisco, Mitchell, Tom, & Botvinick, Matthew. (2009). Machine learning classifiers and fMRI: a tutorial overview. *NeuroImage, 45*(1), S199-S209.

Pietrobelli, Angelo, Faith, Myles S, Allison, David B, Gallagher, Dympna, Chiumello, Giuseppe, & Heymsfield, Steven B. (1998). Body mass index as a measure of adiposity among children and adolescents: a validation study. *The Journal of Pediatrics, 132*(2), 204-210.

Poirier, Paul, Giles, Thomas D, Bray, George A, Hong, Yuling, Stern, Judith S, Pi-Sunyer, F Xavier, & Eckel, Robert H. (2006). Obesity and cardiovascular disease: pathophysiology, evaluation, and effect of weight loss an update of the 1997 American Heart Association Scientific statement on obesity and heart disease from the obesity committee of the council on nutrition, physical activity, and metabolism. *Circulation, 113*(6), 898-918.

Prasanth, P Udaya, Revathi, V Solai, & Maheswari, O Uma. (2017). Classification of Healthy and ADHD Subjects Using Neural Network Classifier. *Networking and Communication Engineering, 9*(2), 21-25.

Raji, Cyrus A, Ho, April J, Parikshak, Neelroop N, Becker, James T, Lopez, Oscar L, Kuller, Lewis H, . . . Thompson, Paul M. (2010). Brain structure and obesity. *Human brain mapping, 31*(3), 353-364.

Ravussin, Eric, & Bogardus, Clifton. (2000). Energy balance and weight regulation: genetics versus environment. *British Journal of Nutrition, 83*(S1), S17-S20.

Rolls, Edmund T. (2000). The orbitofrontal cortex and reward. *Cerebral Cortex, 10*(3), 284-294.

Salbe, Arline D, Weyer, Christian, Lindsay, Robert S, Ravussin, Eric, & Tataranni, P Antonio. (2002). Assessing risk factors for obesity between

childhood and adolescence: I. Birth weight, childhood adiposity, parental obesity, insulin, and leptin. *Pediatrics, 110*(2), 299-306.

Sarwer, David B, von Sydow Green, Amy, Vetter, Marion L, & Wadden, Thomas A. (2009). Behavior therapy for obesity: where are we now? *Current Opinion in Endocrinology, Diabetes and Obesity, 16*(5), 347-352.

Seghier, Mohamed L. (2013). The angular gyrus multiple functions and multiple subdivisions. *The Neuroscientist, 19*(1), 43-61.

Smucny, Jason, Cornier, Marc-Andre, Eichman, Lindsay C, Thomas, Elizabeth A, Bechtell, Jamie L, & Tregellas, Jason R. (2012). Brain structure predicts risk for obesity. *Appetite, 59*(3), 859-865.

Soreca, Isabella, Rosano, Caterina, Jennings, J Richard, Sheu, Lei K, Kuller, Lewis H, Matthews, Karen A, . . . Gianaros, Peter J. (2009). Gain in adiposity across 15 years is associated with reduced gray matter volume in healthy women. *Psychosomatic medicine, 71*(5), 485.

Speakman, John R., Levitsky, David A., Allison, David B., Bray, Molly S., de Castro, John M., Clegg, Deborah J., . . . Westerterp-Plantenga, Margriet S. (2011). Set points, settling points and some alternative models: theoretical options to understand how genes and environments combine to regulate body adiposity. *Disease Models & Mechanisms, 4*(6), 733-745. doi: 10.1242/dmm.008698

Stevens, Victoria L, Jacobs, Eric J, Patel, Alpa V, Sun, Juzhong, McCullough, Marjorie L, Campbell, Peter T, & Gapstur, Susan M. (2015). Weight cycling and cancer incidence in a large prospective US cohort. *American journal of epidemiology*, kwv073.

Stice, Eric, Burger, Kyle S, & Yokum, Sonja. (2013). Relative ability of fat and sugar tastes to activate reward, gustatory, and somatosensory regions. *The American journal of clinical nutrition, 98*(6), 1377-1384.

Stice, Eric, Burger, Kyle S, & Yokum, Sonja. (2015). Reward Region Responsivity Predicts Future Weight Gain and Moderating Effects of the TaqIA Allele. *The Journal of Neuroscience, 35*(28), 10316-10324.

Stice, Eric, Marti, C Nathan, Spoor, Sonja, Presnell, Katherine, & Shaw, Heather. (2008). Dissonance and healthy weight eating disorder prevention programs: long-term effects from a randomized efficacy trial. *Journal of Consulting and Clinical Psychology, 76*(2), 329.

Stice, Eric, Spoor, Sonja, Bohon, Cara, Veldhuizen, Marga G, & Small, Dana M. (2008). Relation of reward from food intake and anticipated food intake to obesity: a functional magnetic resonance imaging study. *Journal of Abnormal Psychology, 117*(4), 924.

Stice, Eric, Spoor, Sonja, Ng, Janet, & Zald, David H. (2009). Relation of obesity to consummatory and anticipatory food reward. *Physiology & Behavior, 97*(5), 551-560.

Stice, Eric, Yokum, Sonja, Blum, Kenneth, & Bohon, Cara. (2010). Weight gain is associated with reduced striatal response to palatable food. *The Journal of Neuroscience, 30*(39), 13105-13109.

Stice, Eric, Yokum, Sonja, Bohon, Cara, Marti, Nate, & Smolen, Andrew. (2010). Reward circuitry responsivity to food predicts future increases in body mass: moderating effects of DRD2 and DRD4. *Neuroimage, 50*(4), 1618-1625.

Stice, Eric, Yokum, Sonja, Burger, Kyle S, Epstein, Leonard H, & Small, Dana M. (2011). Youth at risk for obesity show greater activation of striatal and somatosensory regions to food. *The Journal of Neuroscience, 31*(12), 4360-4366.

Tanaka, Saori C, Doya, Kenji, Okada, Go, Ueda, Kazutaka, Okamoto, Yasumasa, & Yamawaki, Shigeto. (2004). Prediction of immediate and future rewards differentially recruits cortico-basal ganglia loops. *Nature neuroscience, 7*(8), 887-893.

Trayhurn, Paul. (2005). The biology of obesity. *Proceedings of the Nutrition Society, 64*(01), 31-38.

Turk, Melanie Warziski, Yang, Kyeongra, Hravnak, Marilyn, Sereika, Susan M, Ewing, Linda J, & Burke, Lora E. (2009). Randomized clinical trials of weight-loss maintenance: A review. *The Journal of cardiovascular nursing, 24*(1), 58.

Tzourio-Mazoyer, Nathalie, Landeau, Brigitte, Papathanassiou, Dimitri, Crivello, Fabrice, Etard, Olivier, Delcroix, Nicolas, . . . Joliot, Marc. (2002). Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. *NeuroImage, 15*(1), 273-289.

van Ginneken, Vincent, Sitnyakowsky, Laura, & Jeffery, Jonathan E. (2009). "Infectobesity: viral infections (especially with human adenovirus-36: Ad-36) may be a cause of obesity. *Medical Hypotheses, 72*(4), 383-388.

Vucetic, Zivjena, & Reyes, Teresa M. (2010). Central dopaminergic circuitry controlling food intake and reward: implications for the regulation of obesity. *Wiley Interdisciplinary Reviews: Systems Biology and Medicine, 2*(5), 577-593.

Wang, Ze, Childress, Anna R, Wang, Jiongjiong, & Detre, John A. (2007). Support vector machine learning-based fMRI data group analysis. *NeuroImage, 36*(4), 1139-1151.

Wangensteen, Teresia, Undlien, Dag, Tonstad, Serena, & Retterstøl, Lars. (2005). [Genetic causes of obesity]. *Tidsskrift for den Norske laegeforening : tidsskrift for praktisk medicin, ny raekke, 125*(22), 3090-3093.

Whitaker, Robert C, Wright, Jeffrey A, Pepe, Margaret S, Seidel, Kristy D, & Dietz, William H. (1997). Predicting obesity in young adulthood from childhood and parental obesity. *New England Journal of Medicine, 337*(13), 869-873.

Willette, Auriel A, & Kapogiannis, Dimitrios. (2015). Does the brain shrink as the waist expands? *Ageing research reviews, 20*, 86-97.

Wing, Rena R, Crane, Melissa M, Thomas, J Graham, Kumar, Rajiv, & Weinberg, Brad. (2010). Improving weight loss outcomes of community interventions by incorporating behavioral strategies. *American journal of public health, 100*(12), 2513-2519.

Winter, Samantha R, Yokum, Sonja, Stice, Eric, Osipowicz, Karol, & Lowe, Michael R. (2017). Elevated reward response to receipt of palatable food predicts future weight variability in healthy-weight adolescents. *The American journal of clinical nutrition*, ajcn141143.

Yamasue, H, Kasai, K, Iwanami, A, Ohtani, T, Yamada, H, Abe, O, . . . Furukawa, S. (2003). Voxel-based analysis of MRI reveals anterior cingulate gray-matter volume reduction in posttraumatic stress disorder due to terrorism. *Proceedings of the National Academy of Sciences, 100*(15), 9039-9043.

Yokum, S, Ng, J, & Stice, E. (2012). Relation of regional gray and white matter volumes to current BMI and future increases in BMI: a prospective MRI study. *International journal of obesity, 36*(5), 656-664.

Yokum, Sonja, Gearhardt, Ashley N, Harris, Jennifer L, Brownell, Kelly D, & Stice, Eric. (2014). Individual differences in striatum activity to food commercials predict weight gain in adolescents. *Obesity, 22*(12), 2544-2551.

Yokum, Sonja, Ng, Janet, & Stice, Eric. (2011). Attentional bias to food images associated with elevated weight and future weight gain: an fMRI study. *Obesity, 19*(9), 1775-1783.

Zhang, Xian, Yaseen, Zimri S, Galynker, Igor I, Hirsch, Joy, & Winston, Arnold. (2011). Can depression be diagnosed by response to mother's face? A personalized attachment-based paradigm for diagnostic fMRI. *PloS one, 6*(12), e27253.

Zheng, Huiyuan, & Berthoud, Hans-Rudi. (2008). Neural systems controlling the drive to eat: mind versus metabolism. *Physiology, 23*(2), 75-83.

Vita

Samantha R. Winter

Education

Drexel University, Philadelphia, PA
Candidate for Ph.D. in Applied Cognitive Brain Science
Expected graduation: June 2017
Drexel University, Philadelphia, PA
M.S. in Applied Cognitive Brain Science, 2015
University of Michigan, Ann Arbor, MI
B.A. in Biopsychology, Cognition and Neuroscience, 2012
B.M. in Voice Performance, 2012

Selected Honors and Awards

Nominee, CoAS Promise Award, Drexel Univeristy, 2017
Fellow, The Data Incubator, 2016
Young Investigator Travel Award, The Obesity Society, 2015
Training Fellow, University of Michigan fMRI Training Program, 2014
Fellow, Summer Program For Neuroscience, Ethics and Survival, 2013
Provost Fellow, Drexel University, 2013-2014
James B. Angell Scholar, University of Michigan, 2012
Phi Beta Kappa, University of Michigan 2011-2012
Franklin E. Tillery Scholarship, University of Michigan, 2009-2012
William J. Branstrom Prize, University of Michigan, 2008

Representative Publications

Winter, S. R., Yokum, S., Stice, E., Osipowicz, K., & Lowe, M. R. (2017). Elevated reward response to receipt of palatable food predicts future weight variability in healthy-weight adolescents. *The American Journal of Clinical Nutrition*, *105*(4), 781-789.

Berner, L. A., Winter, S. R., Matheson, B. E., Benson, L., & Lowe, M. R. (2017). Behind binge eating: A review of food-specific adaptations of neurocognitive and neuroimaging tasks. *Physiology & Behavior*.

Winter, S.R., Feig, E.H., Erickson, B., Berkowitz, S., Kounios, J., Lowe, M.R. (2016). The relation of hedonic hunger and restrained eating to lateralized frontal activation. *Physiology & Behavior*, 163, 64-69.

Lowe, M. R., Feig, E. H., **Winter, S. R.,** & Stice, E. (2015). Short-term variability in body weight predicts long-term weight gain. *The American journal of clinical nutrition*, ajcn115402.

Ely, A. V., **Winter, S.R.,** & Lowe, M. R. (2013). The generation and inhibition of hedonically-driven food intake: Behavioral and neurophysiological determinants in healthy weight individuals. *Physiology & Behavior*, 121, 25-34.